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Injectable Shear-Thinning Hydrogels Prevent Ischemic Mitral Regurgitation and Normalize Ventricular Flow Dynamics

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Abstract

Objectives: Injectable hydrogels are known to attenuate left-ventricular (LV) remodeling following myocardial infarction (MI), dependent on material mechanical properties. The effect of hydrogel injection on ischemic mitral regurgitation (IMR) resultant from LV remodeling remains relatively unexplored. This study uses multiple imaging methods to evaluate the efficacy of injectable hydrogels with tunable modulus to prevent post-MI development of IMR.

Methods: Posterolateral MI was induced in twenty sheep with subsequent epicardial injection of saline (control (MI); n=7), soft hydrogel (guest-host crosslinking (GH), modulus<1kPa, n=7), or stiff hydrogel (dual-crosslinking (DC), modulus=41.4±4.3kPa, n=6) within the infarct region and 8-week follow-up. IMR and valve geometry were assessed by echocardiography. LV geometry (long-axis dimension (LAD), posterior chordae length (PCL)) and ventricular flow dynamics were assessed by magnetic resonance imaging.

Results: IMR developed in MI controls at 8 weeks, and was attenuated with hydrogel treatment (IMR grade for MI: 1.86±0.69; GH: 1.29±1.11; DC: 0.50±0.55, P=0.02 vs MI). Tethering of the posterior leaflet increased in MI controls, but not with stiff hydrogel treatment. Across cohorts, IMR was correlated with changes in the LAD (Spearman R=0.77) and PCL (Spearman R=0.64). Intraventricular flow dynamics were highly disturbed in MI controls, but stiff hydrogel treatment normalized flow patterns and reduced the prevalence of large (2+ MR, >5 mL) regurgitant volumes.

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Conclusions: Injectable hydrogels attenuated subvalvular remodeling and leaflet tethering, preventing IMR development and normalizing LV flow dynamics. Hydrogels with a supraphysiological modulus yielded best outcomes.

Graphical abstract

Central Picture: Stiff hydrogels prevent subvalvular remodeling and ischemic mitral regurgitation (IMR).

Central Message: Intramyocardial hydrogel injection prevents subvalvular remodeling and leaflet tethering, thereby preventing development of mitral regurgitation.

Keywords

remodeling; mitral valve regurgitation; magnetic resonance imaging; echocardiography; intervention; hydrogel

Introduction

Following myocardial infarction (MI), left-ventricular (LV) remodeling^{1, 2} can precipitate development of congestive heart failure (CHF) which may be compounded by ischemic mitral regurgitation (IMR) (Figure 1A,B). While the leaflets themselves are normal, IMR is associated with variable degrees of LV enlargement, annular dilatation, papillary muscle displacement and leaflet tethering.^{3–5} The sum of these geometric changes is malcoaptation of the valve leaflets which presents as mitral regurgitation. IMR is observed in nearly 20% of patients post-MI and in greater than 50% of patients with CHF.^{6, 7} There is a graded relationship between mortality and IMR severity,⁸ and patients with moderate-to-severe IMR have a mortality of 50% at 3 years.⁹ Intervention typically occurs subsequent to LV remodeling and IMR development, and valve repair with reduction annuloplasty or valve replacement remain the most common approaches. Yet, neither has demonstrated increased longevity, and reduction annuloplasty is associated with a 30% recurrence rate of IMR,^{10, 11} motivating the development of alternative prophylactic therapies.

Toward this goal, our group has focused on developing therapies that can be administered early after MI with the intent of limiting LV remodeling and thereby preventing IMR development. We have developed and recently reported the use of a novel shear-thinning hydrogel system to limit adverse LV remodeling when delivered into the infarct early after

MI.¹² In the present study, we expand upon this work by exploring the prevention of IMR as it directly relates to subvalvular remodeling and LV flow dynamics. Specifically, we investigated the prevention of IMR by intramyocardial injection of two hyaluronic acid (HA) based biomaterials in an ovine model of posterolateral infarct. These included a soft (guest-host, GH) hydrogel formed by physical crosslinks and which allowed shear-thinning (for injection) and a stiff (dual-crosslinking, DC) hydrogel which allowed similar shear-thinning injection with additional covalent crosslinking in vivo (to achieve a supraphysiological modulus). We hypothesized that the delivery of hydrogels early post-MI would attenuate subvalvular remodeling and leaflet tethering, thereby mitigating IMR development and normalizing LV flow dynamics (Figure 1C,D) and that the outcomes would be dependent on the hydrogel modulus.

Methods

Hydrogel preparation.

To form GH hydrogels through supramolecular interaction,^{13, 14} HA was separately modified with adamantane or β -cyclodextrin. To form DC hydrogels,¹⁵ HA was modified by both adamantane and thiols or β -cyclodextrin and methacrylates. Hydrogels were prepared at 4.5wt% in PBS. Moduli of 799.2 Pa and 41.4 $\pm$ 4.3 kPa have been previously reported for GH and DC hydrogels, respectively.¹²

Ovine infarct model.

Protocols were approved by the University of Pennsylvania's Institutional Animal Care and Use Committee and complied with the National Institute of Health's guidelines for the care and use of laboratory animals (NIH Publication 85–23, revised 1996). Data was collected in the course of prior study.¹² Briefly, adult male Dorset sheep (~45 kg) were assigned into treatment groups consisting of saline (MI control, n=7), soft hydrogel (GH treatment, n=7), and stiff hydrogel (DC treatment, n=6). Group assignment was randomly performed, and researchers were blinded to group allocation throughout procedures. Under anesthesia (1.0–2.0% isoflurane, induced by 25 mg/kg ketamine), left thoracotomy was performed to expose the heart and permanent ligation of select obtuse marginal branches produced a posterolateral infarct comprising ~20% of the LV. Papillary occlusion was confirmed by 2D echocardiography, and animals received 16 epicardial injections (0.3 mL each of saline, GH, or DC) into the infarct region at 30 minutes following ligation. Animals were monitored throughout the surgical procedures by electrocardiography (ECG). The surgical site was closed in layers and postoperative analgesia provided (25–75 μ g transdermal fentanyl).

Echocardiography.

Two-dimensional (2D) Doppler flow and three-dimensional (3D) echocardiography of the mitral valve were performed (iE33; Philips Medical; Andover, MA) at baseline (pre-ligation), 30 minutes post-ligation (post-MI), post-injection, and at 8 weeks. IMR was quantified by a blinded observer using a standardized, semi-quantitative scale.^{16, 17} Intra-observer differences were not examined. The area of the regurgitation jet in the left atria was quantified as a percentage of the total atrial area in the four chamber view, according to the grading scale of 0: no MR, 1+: less than 20%, 2+: 20–40%, 3+: 40–60%, and 4+: <60%.

Mid-systolic mitral valve geometry was assessed by techniques previously described, using Echo-View (TomTec Imaging Systems; Munich, Germany) for 3D reconstruction in conjunction with customized programming.¹⁷

Magnetic resonance imaging and analysis.

Imaging was performed (3T Tim Magnetom Trio; Siemens; Washington DC) at baseline (immediately preceding infarct induction) and at 8 weeks. Anesthesia was maintained throughout imaging, with cardiac gating by placement of a LV pressure catheter (Millar Instruments; Houston, TX). Both MRI and echocardiographic analysis were performed under hemodynamically stable conditions, and without externally controlled preload or afterload conditions.

Regurgitation volumes were determined from MRI. Planar magnitude and phase images were acquired (8 wk) orthogonal and superior to the mitral valve (field of view = 300×243.75 mm, acquisition matrix = 192×117 pixels, slice thickness = 4 mm, repetition time = 41.35 ms, echo time = 3.41 ms, BW = 389 Hz/pixel, flip angle = 25°). Blinded quantification of the net regurgitant volume was performed by automated segmentation of the MV and integration of flow (Argus, Siemens).

Examination of subvalvular remodeling was performed by a blinded researcher, including the long-axis dimension (LAD) and posterior chordae length (PCL), was enabled by CINE MRI data. Images were acquired (0, 8 wk) spanning from the apex to base (field of view = 280×166.25 mm, acquisition matrix = 256 × 152 pixels, slice thickness = 4 mm, repetition time = 27.52 ms, echo time = 1.46 ms, BW = 930 Hz/pixel) The end-systolic phase was isolated (ImageJ; NIH; Bethesda, MD) to provide long-axis sections through the posterior papillary, apex, and mitral valve. The LAD was measured as the length from the base (plane bisecting the LV-LA and Septal-RA junctions) to the endocardial wall of the apex (Figure 3A, top). The PCL was measured as the length from the most prominent point of the posterior papillary to the center of the mitral valve (Figure 3A, bottom).

Four-dimensional flow MRI (4DFlow) was performed at 8 weeks (field of view = 320×320 mm, acquisition matrix = 160×160 pixels, slice thickness = 2 mm, repetition time = 20.8 ms, BW = 460 Hz/pixel, flip angle = 8°). Data underwent noise correction, anti-aliasing, and eddy-current correction where necessary using custom programming (MATLAB; MathWorks; Natick, MA).¹⁸ Visualization of the flow profiles was then performed (EnSight; Computational Engineering International; Apex, NC).

Statistical analysis.

Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software Inc.; La Jolla, CA). Data is presented as mean ± standard deviation (SD). Comparisons were made by one-way (between groups) or two-way (between groups, repeated measures) ANOVA with post hoc Tukey's honest significant difference test. Normality of data was confirmed by Shapiro-Wilk normality test. In the case of non-normal data, results were analyzed by Kruskal-Wallis with post hoc Dunn's multiple comparison test, and data are presented as mean ± interquartile range (IQR). Significance was determined at $\alpha = 0.05$.

Results

Procedural Tolerance.

Throughout the procedures, arrhythmia was monitored by ECG. Upon infarct induction, expected pronounced ST-elevation was observed. In two cases, animals died intraoperatively of ventricular fibrillation prior to injection. A single surviving animal in the GH treatment group required intraoperative defibrillation for correction of rhythm. Arrhythmia was not induced by hydrogel injection in otherwise stable animals, and arrhythmia resulting from MI was not notably exacerbated by hydrogel injection.

Mitral Regurgitation Severity.

2D Doppler echocardiography (Figure 2A) was used to assess progression of MR due to acute MI and injection, as well as chronic remodeling. A duration of 8 weeks was examined in these studies, as prior development of this animal model has demonstrated reliable development of MR over this period and longer study frequently results in end stage heart failure and premature death.¹⁹ The individual changes in MR throughout the study duration (Figure 2B) demonstrate a clear propensity for increased MR grade in control and GH treated cohorts. In contrast, DC treated animals generally displayed no increase in MR grade. At baseline, post-MI, and post-injection, there were no significant differences in IMR severity between groups (Kruskal-Wallis $P>0.55$), and no significant change in IMR occurred within groups between baseline and post-injection (Figure 2C,D, Kruskal-Wallis $P>0.04$). MR progressed from infarct induction to the 8 week timepoint in MI controls (Figure 2E), and progression was prevented by DC hydrogel treatment (Dunn's $P=0.037$). There was a significant difference in IMR between the MI and DC groups at 8 weeks (Dunn's $P=0.027$), and the prevalence of measurable MR was reduced in the DC group. At 8 weeks, four animals in the MI group developed 2+ MR and one developed 3+ MR; two animals in the GH (soft hydrogel) treatment group developed 2+ MR and one developed 3+ MR; in the DC (stiff hydrogel) treatment group, three animals exhibited 1+ MR (two of which were 1+ at baseline) and remaining animals had no detectable MR.

Geometric Remodeling of the Ventricle, Subvalvular Apparatus, and Mitral Valve.

Assessment of LV dilation and its relation to remodeling of the subvalvular apparatus was performed by CINE MRI at end-systole (Figure 3A). Increases in both the LAD and PCL were observed relative to baseline in all groups (Figure 3B), indicative respectively of LV dilation and resultant papillary displacement. Changes in chordae length were well correlated with LV dilation ($PCL = 0.67(LAD) + 1.96$; Pearson $R = 0.76$). Changes in both LAD and PCL dimensions were attenuated by hydrogel treatments at 8 wk, which was significant for DC ($LAD: P=0.079$, $PCL: P=0.013$; Tukey) but not GH ($LAD: P=0.61$, $PCL: P=0.44$; Tukey) treatments. At 8 weeks, changes in these dimensions were positively correlated with the observed MR grade across all groups ($LAD: Spearman R=0.77$, $PCL: Spearman R=0.64$), with treatment-dependent clustering (indicated, Figure 3C).

Global metrics of valve geometry (Table 1) increased in MI controls; while not significant, changes were generally attenuated by hydrogel treatments. Relative to the post-injection geometry, MI control and GH treatment cohorts demonstrated tethering of the mitral leaflets

at 8 weeks, which was absent in the DC treatment group (Figure 4A). Tethering angle (α_H) of the anterior (A1, A2, A3) and posterior (P1, P2, P3) leaflets indicated increased tethering of the posterior leaflet in MI controls that was moderately reduced in GH and significantly reduced (P1, Tukey $P=0.014$) or absent in DC treatments (Figure 4B). The location of strongest tethering in MI controls (P2, P3) was consistent with asymmetric IMR.

Ventricular Flow Dynamics.

4D flow patterns were examined at 8 weeks, including at mid-diastole and end-systole in order to visualize ventricular filling and IMR, respectively. Healthy controls (left) illustrate typical flow patterns, which include an apically directed central jet and both anterior and posterior vortices in diastole and aortic, but not mitral regurgitant flow, in systole. In diastole (Figure 5A), MI controls exhibited a primary jet directed toward the inferior wall, loss of posterior vortices, and turbid flow centralized to the base. Flow was similarly disturbed following GH treatment, with the formation of only weak anterior vortices and minimal apical filling. Healthy ventricular filling patterns were observed in DC cases, with an expectant central jet directed apically and both anterior and posterior vortices observed. During systole, MR was observed for MI and GH cases, but not with DC treatment (Figure 5B), and peak aortic velocity was improved with DC treatment (MI: 0.91 ± 0.13 m/s; GH: 0.89 ± 0.07 m/s; DC: 0.96 ± 0.04 m/s, not significant).

Mitral Regurgitation Affects Functional Measures.

Regurgitant flow was detected by flow velocity and magnitude scans superior to the mitral valve (Figure 6A). The location of the MR jet was consistent with posterolateral infarct and was similar across cases where MR was observed. Quantification of the regurgitation volume (Figure 6B) showed increased prevalence of high volumes (>5 mL) in the MI group (2 of 7 cases, compared to 1 in the GH and 0 in the DC treatment groups). Regurgitation volumes were as high as 17.3 mL. Differences between group means were not significant, likely due to variations in the location of the acquired plane resulting in false negative measurement.

Discussion

The present study builds upon existing knowledge in the field. First, it confirms prior findings in a separate model that differs both in injection location and the materials examined.²⁰ Importantly, the injections here were distributed throughout the infarct region rather than a single bolus injection, which is believed to more effectively stabilize the infarct region. In addition, this work adds to the knowledge that attenuation of IMR development (i) is dependent on hydrogel stiffness, (ii) prevents development of abnormal ventricular flow known to increase the myocardial workload, and (iii) is associated with mitigation of geometric remodeling of the subvalvular apparatus.

Role of Therapeutic Hydrogel Injection Post-MI.

Biomaterial injection has been extensively examined toward treatment of MI,^{21, 22} with most of these materials resulting in mechanical stabilization of the infarct through local modulation of the infarct's mechanical properties.^{23, 24} Recent clinical trials demonstrate

varying degrees of therapeutic efficacy.²⁵ In some cases, similar mechanical interventions (e.g., neocollagenesis,²⁶ epicardial restraints²⁷, and papillary displacement²⁰) have demonstrated reduced IMR development. Yet, much less is known regarding the effects of hydrogel injection therapies on mitral valve remodeling and IMR.

In this study, we examined a therapeutic strategy designed to attenuate LV remodeling and thus mitigate IMR development, where hydrogels were designed specifically to address the therapeutic needs. These included a soft GH hydrogel which underwent shear-thinning (i.e. flows easily through a needle or catheter) to enable delivery within the infarcted region. The DC hydrogel underwent an additional secondary crosslinking reaction that occurred following injection, to stiffen the hydrogel *in situ*. This process was deliberate, as hydrogels with supraphysiological modulus have shown improve therapeutic efficacy toward abating LV remodeling.^{12, 28}

Alterations in ventricular and valvular remodeling were correlated. Specifically, elongation of the LAD (indicative of LV dilation) was attenuated by hydrogel therapy in a stiffness dependent manner, resulting in similar and well-correlated alterations in PCL. The net effect of attenuated remodeling was a concurrent reduction in region-specific mitral tethering and prevention of IMR. Taken together, the results demonstrate the ability of hydrogel injection to limit LV dilation – the underlying cause of IMR development and recurrence⁴ – and thereby mitigate IMR development. The therapy is a uniquely conceived prophylactic therapy, addressing the etiology of IMR development.

Moreover, the present study also examined the interrelation of LV and mitral function. Interestingly, ventricular flow dynamics were highly altered in untreated MI and GH treated groups, demonstrating highly turbid diastolic filling which was constrained to the base and which prevented formation of vortices known to contribute substantially to energy conservation.²⁹ In these cases, loss of kinetic energy due to viscous dissipation may increase the workload on the already damaged tissue; whereas, preservation of healthy flow patterns in DC cases may contribute to observed relative improvements in peak aortic velocity as well as previously reported improvements in stroke volume and ejection fraction.¹² In the setting of chronic heart failure, mitral dysfunction is a major contributing factor to loss of LV function which should be examined in therapeutic approaches aimed toward LV remodeling. As summarized in the **Central Figure**, the present study emphatically demonstrates, through multiple state of the art imaging modalities, that intramyocardial injection of stiff hydrogels in the post-MI setting attenuates initial remodeling of the subvalvular apparatus, reduces mitral tethering, and thereby prevents development of mitral regurgitation and improves LV function.

Clinical Implications.

The results of this study demonstrate the potential of shear-thinning hydrogels with a stiff modulus to limit remodeling of the left ventricle, subvalvular apparatus, and mitral valve when administered into the infarct early after coronary occlusion. These structural changes are associated with significant improvements not only in mitral regurgitation, but also LV flow dynamics and contractile function.³⁰ While our group has previously demonstrated the potential of infarct modification and restraint technologies to limit the development of IMR,

the current study breaks important new ground in two ways. First, the current study demonstrates the effect on subvalvular remodeling and LV flow dynamics which has not been previously described in other studies directed at preventing IMR via infarct modification or restraint. Second, the rheological properties of the material system used in this study have been demonstrated to be amenable to delivery via catheters that can reach the infarct via a percutaneous route. This property used in conjunction with clinically available infarct mapping technologies³¹ will greatly facilitate clinical translation of this exciting new therapeutic paradigm.

In the setting of chronic heart failure, IMR has a drastic negative impact on clinical prognosis. Early intervention in asymptomatic but at-risk patients may uniquely enable the prevention of disease progression, and methods such as prophylactic mitral reconstruction have been advocated for in certain cases to prevent LV dysfunction.³² To achieve clinical impact, however, identification of patients at high risk of IMR development is of utmost importance. Patients suitable for prophylactic intervention may include those which are both i) at high risk for IMR development and ii) undergoing concurrent surgical (e.g., CABG) or percutaneous (e.g., angioplasty) interventions during which hydrogel injections may be performed. Patients at high risk for IMR may be identifiable through clinical prognosis dependent on infarct location or existing predictive metrics which include interpapillary distance, impaired interpapillary fractional shortening, and mitral tethering height.^{33–35} Our study shows that LV hydrogel injection following posterolateral MI attenuates LV remodeling and leaflet tethering and may therefore play an important role in the prophylactic (or early) treatment of patients at high risk of IMR by methods such as these.

Given the morbidity and mortality of untreated IMR as well as the suboptimal results associated with current surgical approaches to the disease, the current study provides important proof of concept for clinically translatable, novel therapeutic paradigm directed at one of the most vexing problems facing surgeons and cardiologists today.

Study Limitations.

Toward the limitations of the study design, invasive clinical intervention within the first days post-MI is likely to be limited by hemodynamic instability. Hydrogel injection was however performed soon after infarct induction. This study therefore demonstrates the potential of hydrogel injection to act as a preventative intervention; though, exploration of injection at later time points remains unexplored. Movement toward animal models inclusive of coronary reperfusion and percutaneous hydrogel injection will be instrumental toward this next step, as they are better representative of percutaneous coronary interventions expected in a clinical setting. Additionally, the model of IMR examined herein represents asymmetric MR resultant from posterolateral MI and moderate MR grade. While this model is clinically relevant, only the posterior papillary is affected. Future studies may focus on broader applicability of hydrogel-based interventions, for example in models of global LV remodeling, symmetric IMR resulting from dilated cardiomyopathy, and models with higher degrees of IMR (e.g., previously developed chronic IMR).

Toward limitations of the imaging methods employed, phase and magnitude scan quantification may under represents the group regurgitant volumes. Due to variation in the

distance of the acquisition plane from the mitral valve, false negative measurement is possible. This is corroborated by an increased prevalence of high MR grades observed by Doppler flow echocardiography at 8 weeks in MI and GH groups, relative to those observed by MRI. In the future, improved methods may be possible by acquisition of multiple plains spanning the mitral valve and left atrium.

Conclusion

Multimodal imaging revealed that LV hydrogel injection attenuated remodeling of the subvalvular apparatus and related development of IMR following posterolateral MI, contributing to improved LV function 8 weeks post-MI. Outcomes were highly dependent on material stiffness, with improved outcomes for stiffer DC hydrogels.

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Abbreviations:

DC	dual-crosslinking
GH	guest-host
IMR	ischemic mitral regurgitation
LV	left ventricle
LAD	long-axis dimension
MI	myocardial infarction
PCL	posterior chordae length

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Perspective:

Ischemic mitral regurgitation (IMR) is a major contributor to chronic heart failure after infarct. We investigated the intramyocardial injection of hydrogels to mitigate subvalvular remodeling and thereby prevent IMR development. Hydrogels with supraphysiological modulus are a promising therapeutic approach to limit IMR.

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Figure 1.

Schematic representation of the influence of hydrogel injection on LV remodeling and ischemic mitral regurgitation (IMR). Posterolateral infarct (i) at baseline (A) and following left-ventricular (LV) remodeling (B) where ventricular dilation and associated posterior papillary displacement (ii) results in asymmetric mitral leaflet tethering and retrograde flow to the right atrium (iii). Treatment by hydrogel injection (C, iv) attenuates LV remodeling (D) and prevents IMR (expanded).

Figure 2.

Assessment of mitral regurgitation (MR) severity following myocardial infarct (MI). (A) Representative 2D Doppler echocardiography (MI control, 8 wk; IMR jet encircled in red) and (B) corresponding changes in MR quantification for animals before infarct (baseline) and 8 weeks after infarct (terminal) with treatment of saline (MI), soft hydrogel (GH), and stiff hydrogel (DC). Acute change in MR as a result of MI (C; baseline to post-MI) and injection (D; post-MI to post-injection). Chronic progression of MR throughout LV remodeling (E; post-injection to 8 wk). Data are presented as median (line), mean (+), IQR (box), and range (whiskers). * $P < 0.05$, n.d.=no difference; Kruskal-Wallis, Dunn's multiple comparison. Indicated: left ventricle (LV), left atrium (LA).

Figure 3.

Geometric changes due to left-ventricular (LV) remodeling. (A) Long-axis dimension (LAD, top) and posterior chord length (PCL, bottom) were determined from CINE MRI. Inset: short-axis views from within the plane of the posterior papillary, indicating the position of long-axis views which were used in measurement. Indicated: aorta (Ao), left atrium (LA), left ventricle (LV), right ventricle (RV), long-axis dimension (LAD) and posterior chord length (PCL). (B) Corresponding quantification for change (, relative to animal baseline) in LAD (top) and PCL (bottom) with treatment of saline (MI), soft hydrogel (GH), and stiff hydrogel (DC). Data are presented as median (line), IQR (box), and range (whiskers).

*P<0.05, n.d.=no difference; ANOVA, Tukey HSD. (C) MR dependence on LAD and PCL at 8 wk, where treatment group clustering is indicated for clarity (MI: black, solid; GH: purple, dashed; DC: green, dotted line).

Figure 4. Geometric changes of the mitral valve. **(A)** 3D echocardiography rendering of the posterior (green) and anterior (red) mitral leaflets (inset: superior view) with treatment of saline (MI), the soft hydrogel (GH), and the stiff hydrogel (DC). Indicated: leaflet deformation (▼). **(B)** Regional quantification of change (post-injection to 8wk) in leaflet angle (α_H). Data are presented as median (line), IQR (box), and range (whiskers). *P<0.05; ANOVA, Tukey HSD.

Figure 5.

Visualization of left-ventricular (LV) flow dynamics at 8 weeks. **(A)** Mid-diastolic filling pattern. Healthy controls (H) and stiff hydrogel (DC) treatments exhibited counter-rotating anterior and posterior vortices, centered around an apically directed central flow. **(B)** End-systolic flow pattern, illustrating aortic flow derived from the LV, including apical flow only in H and DC cases. MR was observed in control (MI) and soft hydrogel (GH) cases. In H and DC cases, dashed lines indicate no flow across the mitral valve. Indicated: aorta (Ao), left atrium (LA), left ventricle (LV), right ventricle (RV), and local pathline direction (white arrows).

Figure 6.

MRI assessment of regurgitation volume. (A) Representative short-axis magnitude scan transecting the left atrium, superior to the mitral valve. Indicated: regurgitation jet (▼), aorta (Ao), left atrium (LA), and pulmonary vein (PV). (B) Regurgitant volume quantification. Data are presented as median (line), mean (+), IQR (box), and range (whiskers). * $P < 0.05$; ANOVA, Tukey HSD.

Table 1.

Assessment of mitral valve geometry.

Post-Injection / Terminal	MI	GH	DC
Annular Area (mm²)	882±93.1 / 995±202	798±160 / 1023±201	926±131 / 1013±226
Commissural Width (mm)	35.0±2.70 / 37.5±3.98	33.7±4.06 / 37.2±4.03	36.4±3.67 / 39.0±4.39
Septolateral Diameter (mm)	28.8±3.02 / 29.6±3.16	25.9±3.08 / 29.2±2.49	27.8±2.86 / 31.8±2.86
Transverse Diameter (mm)	36.1±2.64 / 39.2±3.48	34.2±3.65 / 38.9±3.67	37.5±3.71 / 41.1±3.82

Data provided as mean ± SD.