SUPPLEMENTAL MATERIAL

Nagata, MVP-Related Mechanics, Fibrosis, and Arrhythmia

Figure S1. Inclusion and exclusion flow diagram.

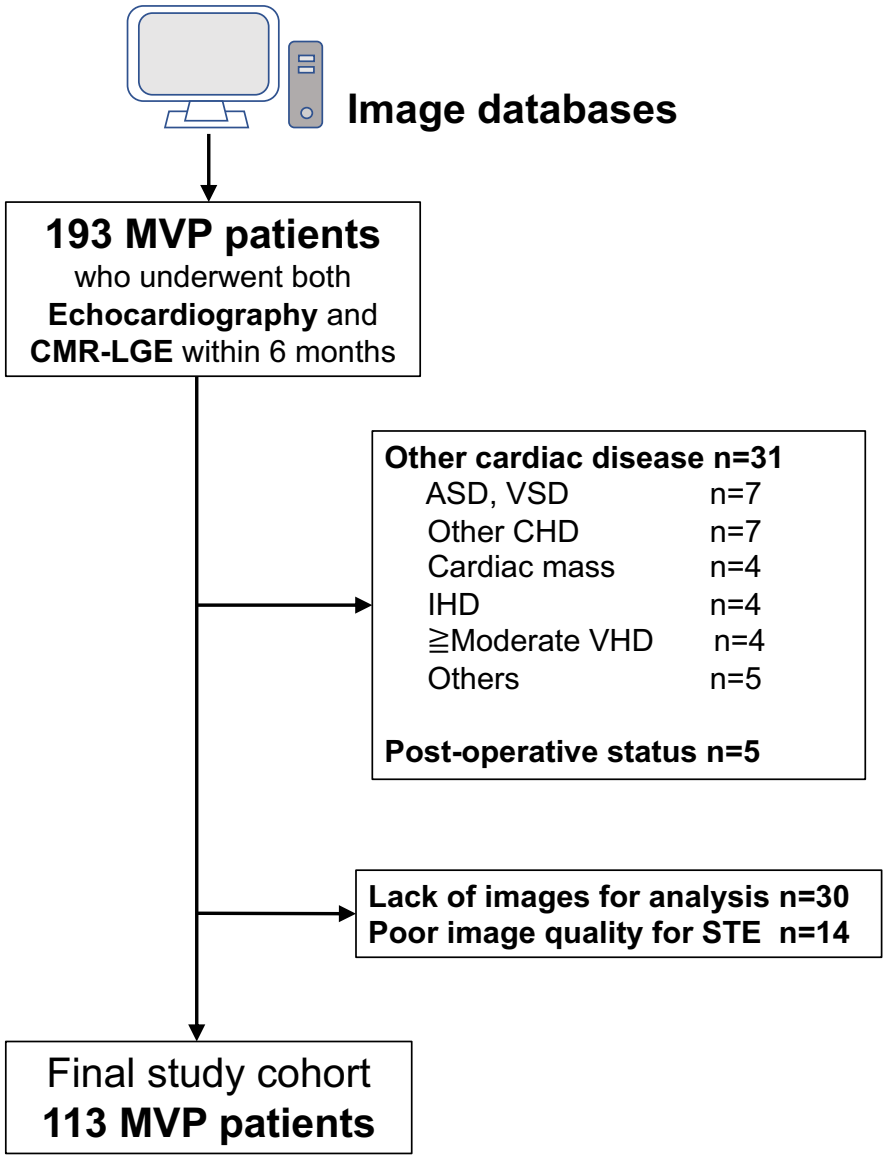


Figure S2. Speckle-tracking echocardiography on the myocardium with the mitral annular disjunction.

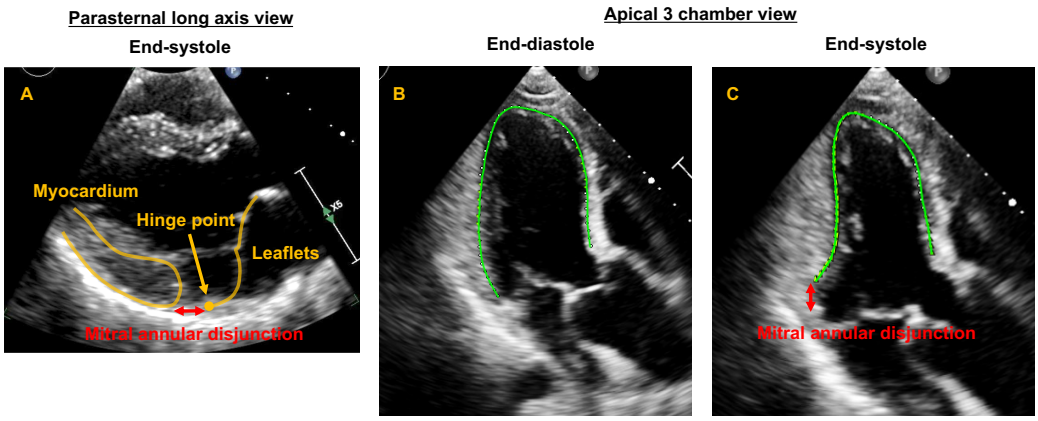


Figure S3. Relation of fibrosis to mitral regurgitation.

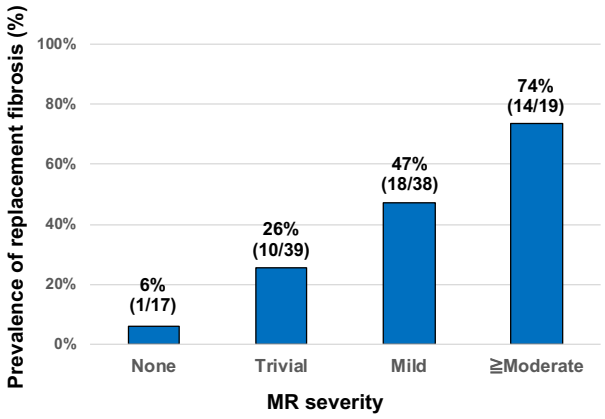


Figure S4. Echocardiographic, strain, and late gadolinium enhancement images in representative cases according to presence of mitral valve prolapse, double-peak strain pattern, and fibrosis.

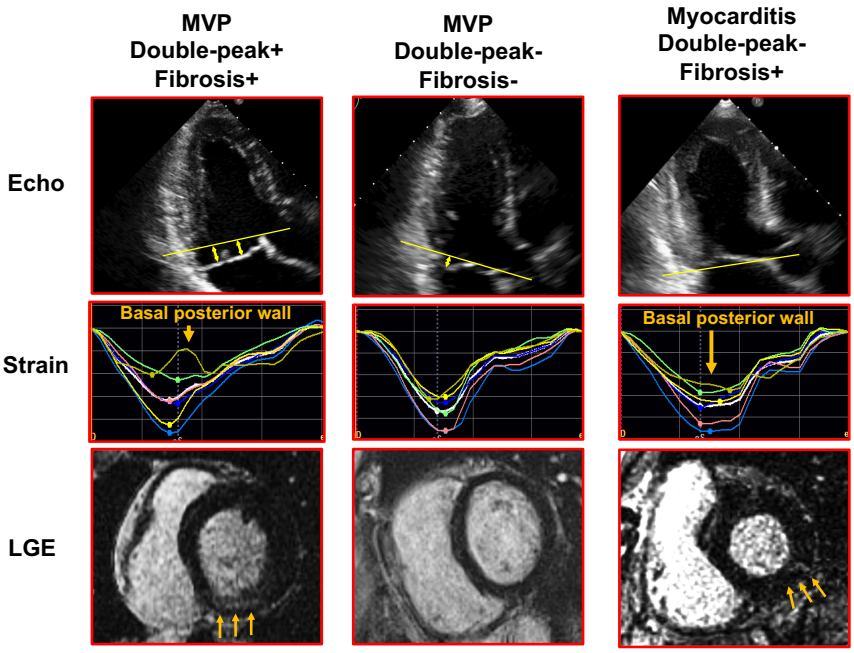


Figure S5. Kaplan-Meier curve for arrhythmic events in subgroups.

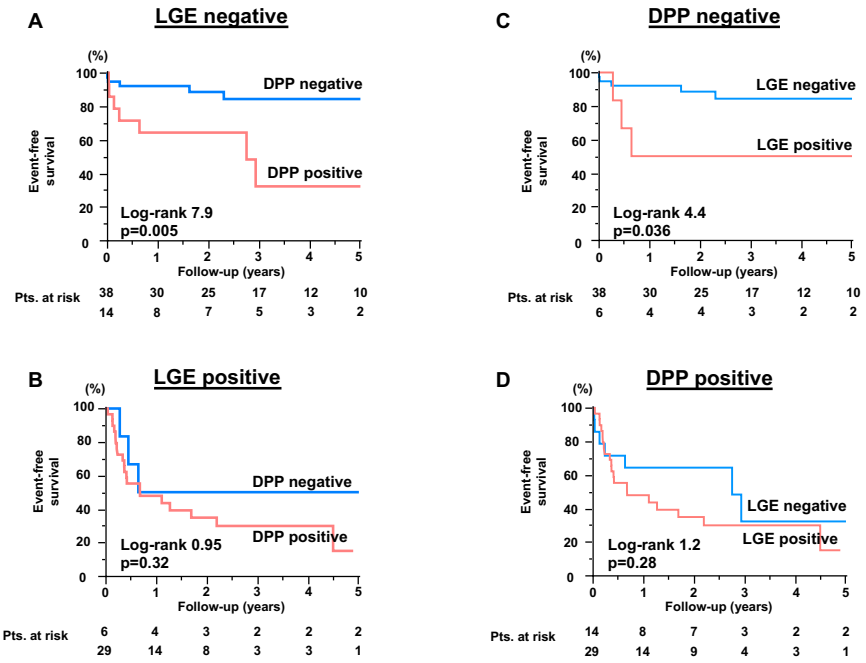
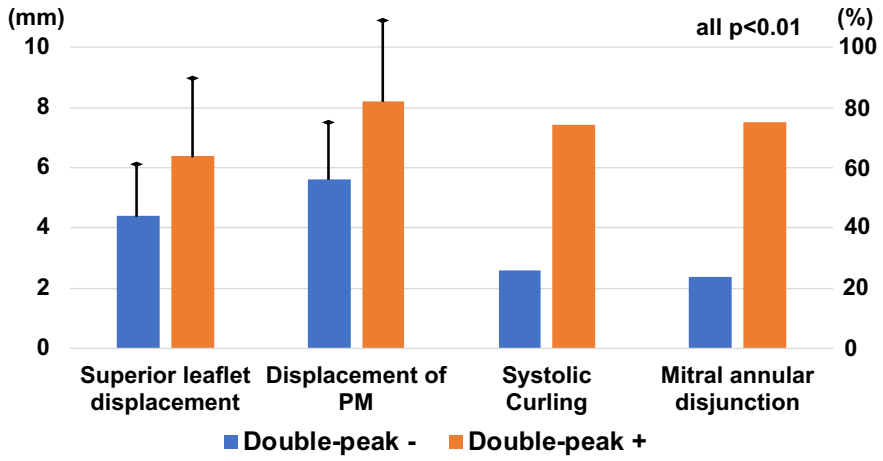


Figure S6. Comparison of mitral valve prolapse-related parameters between patients with versus without double-peak strain pattern.



Supplemental Figures legends

Figure S1. Inclusion and exclusion flow diagram.

ASD, atrial septal defect; CHD, congenital heart disease; CMR-LGE, cardiac magnetic resonance-late gadolinium enhancement; IHD, ischemic heart disease; MVP, mitral valve prolapse; STE, speckle-tracking echocardiography; VHD, valve heart disease

Figure S2. Speckle-tracking echocardiography on the myocardium with the mitral annular disjunction.

Panel A demonstrated the parasternal long axis view in a patient with the mitral annular disjunction. The posterior myocardium is detached from the hinge point of the posterior leaflet (the posterior mitral annulus), showing the mitral annular disjunction (bidirectional arrow). Panel B shows the tracing line (green line) of endocardium at end-diastole in the 3-chamber view. Panel C shows the tracing line (green line) of the endocardium at end-systole without including the gap between the end of the myocardium and the posterior annulus (mitral annular disjunction).

Figure S3. Relation of fibrosis to mitral regurgitation.

The greater mitral regurgitation patients had, the more frequently they had fibrosis.

MR, mitral regurgitation

Figure S4. Echocardiographic, strain, and late gadolinium enhancement images in representative cases according to presence of mitral valve prolapse, double-peak strain pattern, and fibrosis.

Left: Patient with MVP (upper), double-peak strain pattern (middle), and fibrosis in basal inferior to posterior wall (bottom). *Middle:* Patient with MVP, normal strain pattern, and no fibrosis. *Right:* Non-MVP patient with basal posterior wall fibrosis. Middle panels show regional strain curves in apical 3-chamber view.

LGE, late gadolinium enhancement

Figure S5. Kaplan-Meier curve for arrhythmic events in subgroups.

Double-peak strain pattern (DPP) distinguishes patients with from those without arrhythmic events in mitral valve prolapse (MVP) patient group without fibrosis (A), while it does not in the patient group with fibrosis (B). Late gadolinium enhancement evaluation stratifies patients according to the risk of arrhythmic events in MVP patient group without DPP (C), while it does not in the patient group with DPP (D).

DPP = double-peak strain pattern

Figure S6. Comparison of mitral valve prolapse-related parameters between patients with versus without double-peak strain pattern.

Mitral valve prolapse patients with double-peak strain pattern had greater superior displacement of leaflet and papillary muscle and higher prevalence of curling and mitral annular disjunction than patients without double-peak strain pattern.

PM, papillary muscle

Supplemental Tables

Table S1. Comparison of strain in mitral valve prolapse (MVP) vs. Non-MVP with basal inferior-lateral fibrosis.

	MVP with fibrosis n=43	MVP without fibrosis n=70	Non-MVP with fibrosis n=20	p value
Age, yrs	58±16	53±17	48±18	0.088
Sex, male	23 (53%)	376 (51%)	14 (70%)	0.32
LVEDV, ml	153±43	149±50	152±28	0.85
LVESV, ml	61±19	59±25*	74±19	0.039
LVEF, %	61±6*	61±7*	52±9	<0.001
Global longitudinal strain, %	22.4±3.9*	22.9±3.2*	18.7±3.5	<0.001
Mechanical dispersion	5.8±1.7†	4.5±1.3*	6.3±2.5	<0.001
Double-peak strain pattern	35 (81%)*†	18 (26%)*	0 (0%)	<0.001

Statistical significance among 3 groups was determined by one-way ANOVA or Kruskal-Wallis test as appropriate. *p<0.05 vs. non-MVP with basal inferior-lateral fibrosis; †p<0.05 vs. LGE negative. (For continuous variables, Tukey-Kramer test was used for comparing 2 groups among 3; For categorial variables, Chi-squared test or Fisher's exact test was used as appropriate). LVED(S)V = left ventricular end-diastolic (systolic) volume; LVEF = left ventricular ejection fraction

Table S2. Univariable Cox proportional hazard analysis of arrhythmic event in mitral valve prolapse patients (n=87)

Variables	HR	95% Confidence interval	p value
Age, yrs	1.01	0.99 – 1.03	0.37
Sex, male	1.73	0.88 - 3.36	0.11
BSA, kg/m^2	4.10	0.96 - 16.6	0.057
Short of breath	0.22	0.59 - 2.53	0.59
Syncope	2.19	1.04 – 4.58	0.038
NYHA functional classification ≥ II	1.01	0.44 – 2.30	0.99
Hypertension	1.16	0.53 - 2.56	0.71
Diabetes	NA	NA	0.99
Hyperlipidemia	1.47	0.75 – 2.89	0.27
History of heart failure	1.71	0.52 – 5.57	0.34
History of atrial fibrillation	1.87	0.95 - 3.68	0.068
History of ventricular arrhythmia	2.77	1.41 – 5.43	0.003
History of cardiac arrest	3.92	1.50 – 10.2	0.005
β-blocker	1.30	0.68 – 2.51	0.43
Antiarrhythmics	2.53	1.20 – 5.35	0.015
Left ventricular parameters			
LVEDV, ml	1.01	0.99 – 1.02	0.058
LVESV, ml	1.03	1.01 – 1.05	0.003
Left ventricular ejection fraction, %	0.96	0.91 – 1.01	0.081
Global longitudinal strain, %	0.92	0.83 – 1.02	0.12
Basal posterior Post-systolic shortening, %	1.01	0.99 – 1.01	0.11
Basal posterior PSI > 3%	2.24	1.13 – 4.44	0.018
Mechanical dispersion, %	1.15	0.93 – 1.41	0.19

Mechanical dispersion > 5.96%	1.48	0.72 – 3.05	0.28
Double-peak strain pattern	4.81	2.22 – 10.4	<0.001
Mitral valve parameters			
Bileaflet involvement	1.40	0.70 – 2.81	0.34
Superior leaflet displacement, mm	1.14	1.00 – 1.29	0.044
Displacement of papillary muscle, mm	1.14	1.00 – 1.28	0.047
Mitral annular disjunction	2.12	1.06 – 4.26	0.034
Curling	1.69	0.88 – 3.26	0.11
Mitral regurgitation severity ≥ moderate	1.30	0.50 – 3.35	0.59
Late gadolinium enhancement - CMR			
Presence of fibrosis	3.89	1.92- 7.88	<0.001
Medial papillary muscle fibrosis	3.32	1.45 – 7.18	0.004
Lateral papillary muscle fibrosis	1.45	0.51 – 4.13	0.49
LGE quantification, %	1.13	1.05 – 1.20	<0.001

Abbreviations are in Table 1.

Table S3a. Univariable Cox proportional hazard analysis of arrhythmic event in mitral valve patient patients undergoing long-term electrocardiographic monitoring (n=58, event n=32)

Variables	HR	95% Confidence interval	p value
Age, yrs	1.01	0.98 – 1.03	0.54
Sex, male	1.65	0.81 – 3.36	0.16
BSA, kg/m^2	3.66	0.71 – 17.6	0.12
Shortness of breath	1.24	0.56 – 2.77	0.60
Syncope	1.69	0.77 – 3.70	0.21
NYHA functional classification ≥ II	0.99	0.41 – 2.43	0.99
Hypertension	1.64	0.67 – 3.98	0.28
Diabetes	NA	NA	NA
Hyperlipidemia	1.17	0.55 – 2.51	0.68
History of heart failure	1.98	0.47 – 8.30	0.35
History of atrial fibrillation	1.35	0.65 – 2.81	0.42
History of ventricular arrhythmia	2.08	1.00 – 4.33	0.045
History of cardiac arrest	2.93	1.11 – 7.77	0.031
β-blocker	1.14	0.56 – 2.30	0.72
Antiarrhythmics	2.02	0.93 – 4.36	0.074
Left ventricular parameters			
LVEDV, ml	1.01	0.99 – 1.02	0.082
LVESV, ml	1.03	1.01 – 1.05	0.006
Left ventricular ejection fraction, %	0.97	0.93 – 1.02	0.26
Global longitudinal strain, %	0.93	0.83 – 1.04	0.21
Basal posterior Post-systolic shortening, %	1.00	0.99 – 1.01	0.26
Basal posterior PSI > 3%	2.24	1.13 – 4.44	0.021
Mechanical dispersion, %	1.20	0.96 – 1.49	0.11
Mechanical dispersion > 5.96%	1.62	0.76 – 3.49	0.21
Double-peak strain pattern	5.41	2.18 – 13.4	<0.001
Mitral valve parameters			
Bileaflet involvement	1.95	0.93 – 4.05	0.076
Superior leaflet displacement, mm	1.19	1.02 – 1.39	0.022
Displacement of papillary muscle, mm	1.29	1.08 – 1.54	0.004

Mitral annular disjunction	2.21	1.04 – 4.68	0.039
Curling	1.75	0.87 – 3.50	0.12
Mitral regurgitation severity ≥ moderate	1.78	0.68 – 4.63	0.24
Late gadolinium enhancement - CMR			
Presence of fibrosis	4.78	1.93 – 11.8	<0.001
Medial papillary muscle fibrosis	3.16	1.31 – 7.58	0.010
Lateral papillary muscle fibrosis	2.30	0.79 – 6.68	0.13
LGE quantification, %	1.12	1.04 – 1.19	0.002

Abbreviations are in Table 1.

Table S3b. Multivariable Cox proportional hazard analysis of arrhythmic event in mitral valve prolapse patients undergoing long-term electrocardiographic monitoring (n=58, event n=32)

variables	Hazard ratio	95% Confidence interval	p value
	Model 1		
Fibrosis	3.47	1.53 – 7.86	0.003
History of cardiac arrest	1.84	0.68 – 4.98	0.23
	Model 2		
Fibrosis	3.52	1.61 – 7.72	0.002
Left ventricular end-systolic volume	1.02	1.00 – 1.04	0.016
	Model 3		
Fibrosis	3.37	1.47 – 7.69	0.004
Superior leaflet displacement	1.11	0.94 – 1.30	0.22
	Model 4		
Fibrosis	3.74	1.63 – 8.59	0.002
Mechanical dispersion	1.05	0.83 – 1.31	0.69
	Model 5		
Fibrosis	3.91	1.64 – 9.31	0.002
Curling	1.01	0.47 – 2.16	0.99
	Model 6		
Fibrosis	3.43	1.51 – 7.78	0.003
Mitral annular disjunction	1.61	0.74 – 3.51	0.23
	Model 7		
Fibrosis	2.05	0.83 – 5.03	0.12
Double-peak strain pattern	3.67	1.31 – 10.3	0.013
	Model 8		
Fibrosis	3.87	1.72 – 8.71	<0.001
History of arrhythmia	1.95	0.93 – 4.10	0.078
	Model 9		
Fibrosis	2.02	0.81 – 5.07	0.13
Double-peak strain pattern	3.60	1.26 – 10.3	0.017
History of arrhythmia	1.86	0.88 – 3.93	0.10

Table S4. Intra- and inter-observer variability

variables	Intra-observer κ-statistics	Inter-observer κ-statistics
Curling	0.737	0.737

Mitral annular disjunction	0.737	0.865
Double-peak strain pattern	0.857	0.732
	Intraclass correlation coefficient	Interclass correlation coefficient
Global longitudinal strain	0.908	0.835
Mechanical dispersion	0.812	0.749

Supplemental Video legends

Video S1. A representative echocardiogram demonstrating systolic curling motion

Systolic curling is characterized by exaggerated apical systolic motion of the posterior mitral valve annulus and inward excursion of the adjacent posterobasal myocardium along with papillary muscle traction tugged by superior leaflet displacement

Video S2. Speckle-tracking echocardiography at 3-chamber view on the myocardium with the mitral annular disjunction.