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ORIGINAL RESEARCH

VENTRICULAR ARRHYTHMIAS - PATHOPHYSIOLOGY

Arrhythmic Mitral Valve Prolapse With Only Mild or Moderate Mitral Regurgitation

Characterization of Myocardial Substrate

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ABSTRACT

BACKGROUND Sustained ventricular tachycardia and sudden cardiac death due to degenerative mitral valve prolapse (MVP) can occur in the absence of severe mitral regurgitation (MR). A significant percentage of patients with MVP-related sudden death do not have any evidence of replacement fibrosis, suggesting other unrecognized proarrhythmic factors may place these patients at risk.

OBJECTIVES This study aims to characterize myocardial fibrosis/inflammation and ventricular arrhythmia complexity in patients with MVP and only mild or moderate MR.

METHODS Prospective observational study of patients with MVP and only mild or moderate MR underwent ventricular arrhythmia characterization and hybrid positron emission tomography (PET)/magnetic resonance imaging (MRI). Coregistered hybrid $^{18}F^{-}$fluorodeoxyglucose (^{18}F-FDG)-PET and MRI late gadolinium enhancement images were assessed and categorized. Recruitment occurred in the cardiac electrophysiology clinic.

RESULTS In 12 patients with degenerative MVP with only mild or moderate MR, of which a majority had complex ventricular ectopy (n = 10, 83%), focal (or focal-on-diffuse) uptake of ^{18}F-FDG (PET-positive) was detected in 83% (n = 10) of patients. Three-quarters of the patients (n = 9, 75%) had FDG uptake that coexisted with areas of late gadolinium enhancement (PET/MRI-positive). Abnormal T1, T2 and extracellular volume (ECV) values were observed in 58% (n = 7), 25% (n = 3), and 16% (n = 2), respectively.

CONCLUSIONS Most patients with degenerative MVP, ventricular ectopy, and mild or moderate MR show myocardial inflammation that is concordant with myocardial scar. Further study is needed to determine whether these findings contribute to the observation that most MVP-related sudden deaths occur in patients with less than severe MR. (J Am Coll Cardiol EP 2023;9:1709–1716) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

FDG = fluorodeoxyglucose

LGE = late gadolinium enhancement

MR = mitral regurgitation

MVP = mitral valve prolapse

PVC = premature ventricular contraction

VA = ventricular arrhythmia

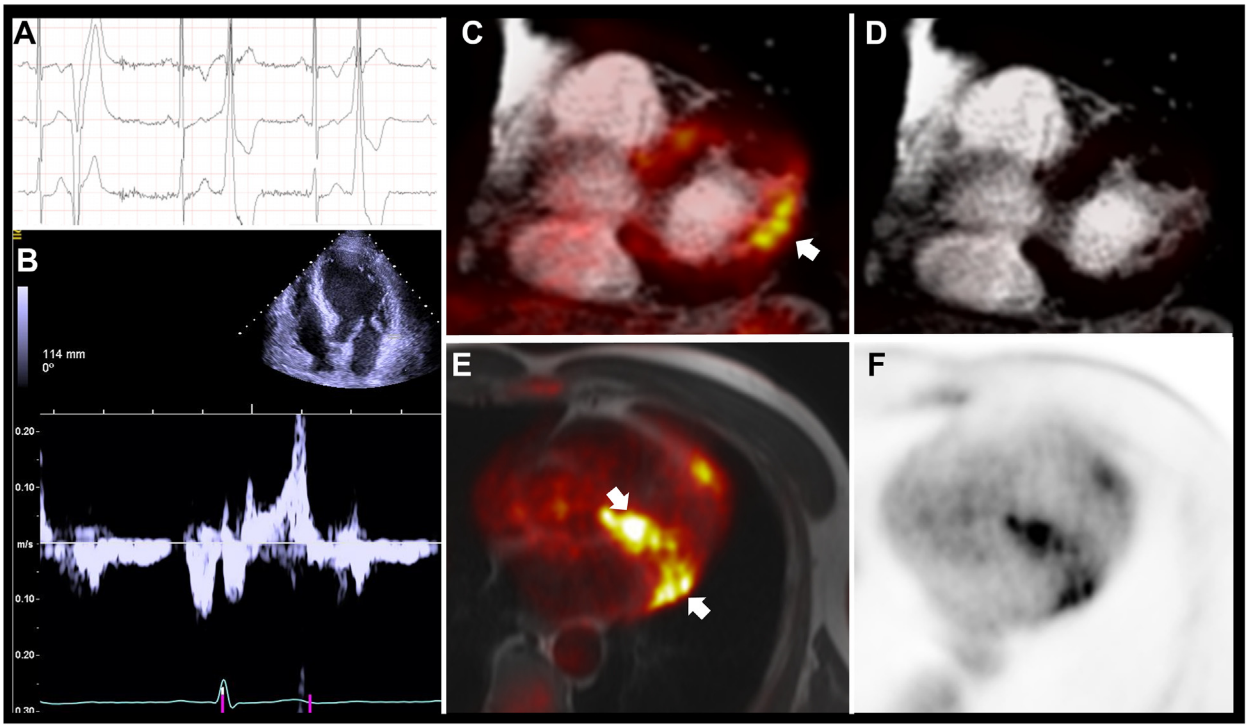
SCD = sudden cardiac death

SUV = standard uptake value

Mitral valve prolapse (MVP) is associated with sustained ventricular arrhythmias (VAs) and sudden cardiac death (SCD). Identified risk factors include sex (female), bileaflet prolapse, complex ventricular ectopy, mitral annular disjunction, and late gadolinium enhancement (LGE) (replacement fibrosis).[1] Although the highest prevalence of replacement fibrosis is identified in patients with severe mitral regurgitation (MR), LGE has also been detected in a significant percentage of MVP patients with only mild (13%) or moderate (28%) MR.[1] In addition, although the presence of LGE in a significant percentage of patients with less-than-severe MR may partially explain the observation that a majority of MVP-related SCDs occur in patients with only mild or moderate MR, approximately one-quarter of patients with MVP-related ventricular tachycardia (VT) and/or SCD do not have any imaging or autopsy evidence of replacement fibrosis.[2-4] A heretofore unrecognized proarrhythmic substrate, such as inflammation, may place patients with less-than-severe MR at risk for sustained VAs.[3,5]

A mechanistic hypothesis for the development of an arrhythmogenic substrate in MVP is valve-induced mechanical stresses that induce both myocardial fibrosis and inflammation.[6,7] Highly sensitive to mechanical forces, fibroblasts activate and proliferate in response to the stimulation of acute stretch forces exerted by the prolapsing leaflet. These activated fibroblasts promote infiltration of immune and inflammatory cells.[8,9] We have shown previously that 18-labeled (^{18}F) fluorodeoxyglucose (FDG) uptake (positron emission tomography [PET]-positive), a surrogate of myocardial inflammation, frequently colocalized to areas of LGE in patients with MVP and severe MR, which implied a relationship between extensive myxomatous valve disease, myocardial inflammation, and ventricular ectopy.[10] However, there remains a knowledge gap as to whether inflammation and fibrosis occur in the absence of

FIGURE 1 Holter, Echocardiography, and Hybrid Positron Emission Tomography/Magnetic Resonance Imaging



A 64-year-old man with bileaflet mitral valve prolapse with mild to moderate mitral regurgitation and palpitations. **(A)** Pleimorphic premature ventricular contractions. **(B)** Transthoracic echocardiography-derived pulsed-wave tissue Doppler of the posterolateral mitral annulus (apical long-axis view) with associated Pickelhaube spike (>16 cm/s). **(C to F)** Fluorine 18-labeled fluorodeoxyglucose (FDG) uptake in the basal left ventricular segments with minimal late gadolinium enhancement. The **white arrowheads** indicate areas of FDG uptake.

significant MR.[11] As such, our current study seeks to characterize myocardial replacement fibrosis, interstitial fibrosis, and inflammation in patients with MVP and only mild or moderate MR and a history of premature ventricular contractions (PVCs).

METHODS

STUDY POPULATION, ECHOCARDIOGRAPHY AND ARRHYTHMIA MONITORING AND CLASSIFICATION. Patients with a degenerative MVP with only mild or moderate MR and a history of PVCs were prospectively enrolled and underwent hybrid PET/magnetic resonance imaging (MRI). Recruitment occurred in the Division of Cardiac Electrophysiology at the Mount Sinai Medical Center, New York, New York, USA. The study was approved by the Mount Sinai Institutional Review Board, and all patients gave written informed consent. Patients were excluded if they had a pacemaker or defibrillator, prior history of catheter ablation for a ventricular arrhythmia, or known sustained VA. MVP was confirmed by transthoracic echocardiography, as previously defined.[12] Transthoracic echocardiographic images were reviewed by a board-certified cardiologist and an echocardiography specialist. The length of mitral annular disjunction was measured from the left atrial wall-mitral valve posterior leaflet junction to the top of the left ventricular (LV) posterior wall during end-systole, as previously described.[13] Pulsed-wave tissue Doppler of the lateral mitral annulus from the apical window was quantified, and a spiked systolic high-velocity signal ≥16 cm/s was considered consistent with a positive "Pickelhaube" sign.[14] Patients underwent ambulatory electrocardiographic event monitoring before the hybrid PET/MRI. Mobile cardiac outpatient telemetry monitoring (7-14 days) was performed in 5 patients and Holter monitoring (24-48 hours) was performed in 7 patients. VAs were categorized as either minor (m-VA) or complex (c-VA), according to the Lown and Wolf classification.[15] mVAs included isolated unifocal PVCs (grade 1 or 2), whereas cVAs included pleomorphic PVCs (grade 3), couplets (grade 4A), and triplets/nonsustained VT (grade 4B). PVC burden was also quantified.

TABLE 1 **Baseline Characteristics, Transthoracic Echocardiography, and Ambulatory ECG Monitoring (N = 12)**

Age, y	57 ± 10.72
Female	8 (66.7)
Transthoracic echocardiography	
LVEDD, mm	48.3 ± 6.23
LVESD, mm	30.3 ± 5.92
LVEF, %	61.8 ± 5.59
Lateral TDI, cm/s	14.12 ± 5.22
Bileaflet mitral valve prolapse	6 (50.0)
Posterior-leaflet mitral valve prolapse	6 (50.0)
Mild mitral regurgitation	7 (58.3)
Moderate mitral regurgitation	5 (41.7)
Mitral annular disjunction	9 (75.0)
Pickelhaube sign	4 (33.3)
ECG and ventricular arrhythmia	
Inverted/biphasic T waves (inferior leads)	3 (25.0)
Atrial fibrillation	1 (8.3)
Syncope	3 (25.0)
PVC burden	5.1 ± 6.8
Complex ventricular ectopy	10 (83.3)
Pleomorphic PVCs	7 (58.3)
Ventricular couplets	8 (66.7)
Nonsustained ventricular tachycardia	6 (50.0)
Minor ventricular ectopy	2 (16.7)

Values are mean ± SD or n (%).

ECG = electrocardiography; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; PVC = premature ventricular contraction; TDI = tissue Doppler imaging.

HYBRID PET/MRI ACQUISITION AND ANALYSIS. Each patient underwent simultaneous cardiac ^{18}F-FDG-PET and MRI with LGE imaging on a hybrid PET/MRI system (Biograph-mMR, Siemens Health-ineers), as previously described.[16] Briefly, patients were administered 5 MBq/kg ^{18}F-FDG before imaging. Patients were required to follow a low-carbohydrate and high-fat diet (starting at least 24 hours before the examination), and to have fasted overnight with a blood glucose <200 mg/dL before the scan.[17] Image data were acquired between 30 and 90 minutes post-injection in a single thoracic imaging volume. Standard breath-held electrocardiogram (ECG)-triggered LGE MRI was performed approximately 10 minutes post-injection of 30 mL gadolinium-based contrast agent (MultiHance [gadobenate dimeglumine] injection, 529 mg/mL, Bracco Diagnostics Inc) in 8-10 short-axis view slices (8-mm thick with 2-mm slice-gap) covering the LV. Co-registered short-axis hybrid ^{18}F-FDG PET and LGE MRI images were then assessed. The average standard uptake values (SUVmean) in each segment of the standard 17-segment American Heart Association model were recorded as well as target-to-background ratio (TBRmean) by normalization of the SUV values to the mean blood pool activity (SUVmean) in the ventricle. The maximum TBR anywhere in the myocardium (TBRmax) was also recorded. Each segment was evaluated as PET^{+} if TBRmean was >1.75, a cutoff determined previously to separate PET^{+} from PET^{-} in cardiac sarcoidosis.[16] The location and value of the maximum SUVmax and TBRmax in the myocardium were recorded. Each American Heart Association segment was designated LGE$^+$ if contrast enhancement was observed. Patients were categorized into the following groups: 1) PET$^+$ and MRI$^+$ when a pattern of increased focal or focal-on-diffuse ^{18}F-FDG uptake coexisted with a pattern of LGE (Figure 1); 2) PET$^+$ and MRI$^-$ if there was increased focal or focal-on-diffuse ^{18}F-FDG uptake without underlying LGE; 3) PET$^-$/MRI$^+$; 4) PET$^-$/MRI$^-$; and 5) physiologic ^{18}F-FDG uptake.[10] T1 mapping used a standard breath-held ECG-triggered inversion-prepared, Look-Locker-based T1 mapping acquisition, with 8 inversion times over 2 preparations in 5-beat- and 3-beat segments with 3 recovery beats between preparations in the same short-axis view slices covering the myocardium as for LGE. T2 mapping used a standard breath-held ECG-triggered acquisition with 3 T2-preparation times (0, 25, and 50 ms) in the same short-axis views. T1 mapping was repeated after LGE image acquisition, after gadolinium contrast administration, to calculate extracellular volume (ECV) also using hematocrit measured from a blood sample drawn at the time of imaging.[18] T1 and T2 maps were generated with dedicated software (cvi42, Circle Cardiovascular Imaging). T1 and T2 values were extracted for basal to mid-LV myocardial segments, and apical segments were excluded from the analysis.[19] ECV maps were automatically generated by the software, and ECV values were extracted for basal to mid-LV myocardial segments. Abnormal T1, ECV, and T2 values were defined when the value of the highest-valued myocardial segment was more than 2 standard deviations above the reference values measured for our site. The reference values were the mean of values measured in 7 normal control subjects. Values greater than the local normal reference values were considered abnormal: 1,045.1 ± 63.6 ms (native T1); 25.0% ± 7.8% (ECV); 44.0 ± 10.6 ms (T2). In addition, standard cine cardiac MRI was used to measure cardiac dimensions and ejection fraction using standard methods with dedicated software (cvi42).

STATISTICS. Descriptive statistics were used to characterize the study population. Continuous variables were summarized as mean ± SD. Categorical variables were presented as n (%). Statistical calculations were performed by using SPSS version 12.0 (SPSS Inc).

RESULTS

As shown in Table 1, most of the patients were female (n = 8, 67%), whereas one-half had bileaflet prolapse (50%, n = 6) and the other half had posterior-leaflet prolapse only. MR was mild in 58% (n = 7) and moderate in 42% (n = 5). Mitral annular disjunction was present in three-quarters of the patients (n = 9, 75%), the mean pulsed-wave tissue Doppler of the lateral mitral annulus was 14.12 ± 5.22 cm/s and a Pickelhaube sign (≥16 cm/s) was detected in one-third (n = 4, 33%) of all the patients.

TABLE 2 Hybrid PET/MRI Findings (N =12)

Classification	
PET$^+$/MRI$^+$	9 (75.0)
PET$^+$/MRI$^-$	1 (8.3)
PET$^-$/MRI$^-$	1 (8.3)
PET$^-$/noncontrast MRI	1 (8.3)
FDG uptake	
PET$^+$	10 (83.3)
Papillary muscle/inferolateral or basal inferior left ventricle	6 (60)
Multifocal	4 (40)
SUVmax	4.75 ± 3.12
TBRmax	3.06 ± 2.36
Concordant FDG and LGE	9 (90)
MRI	
LVEDVi, mL/m^2	85.21 ± 13.56
LVESVi, mL/m^2	35.58 ± 8.92
LVEF, %	58.56 ± 5.77
LV mass indexed, g/m^2	51.32 ± 11.63
LGE	7.21 ± 5.13
T1, ms	1,109.70 ± 45.97
Abnormal T1	7 (58)
ECV	28.21 ± 5.70
Abnormal ECV	2 (16)
T2, ms	48.35 ± 3.44
Abnormal T2	3 (25)

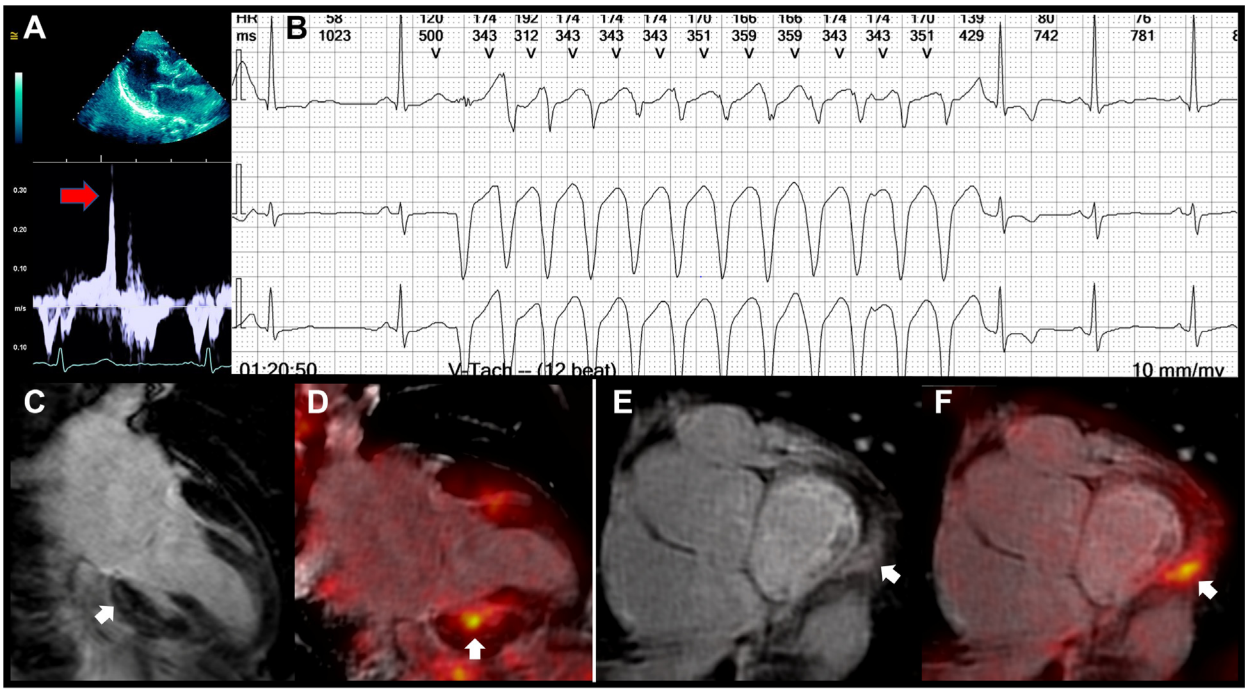
Values are n (%) or mean ± SD.

ECV = extracellular volume; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index; MRI = magnetic resonance imaging; PET = positron emission tomography; SUV = standardized uptake value; TBR = tissue-to-background ratio.

VAs. One-quarter of the patients (n = 3, 25%) had inverted/biphasic T waves in the inferior leads on 12-lead ECG. Most of the patients had cVAs (n = 10, 83%), including pleomorphic PVCs in 58% (n = 7), couplets in 67% (n = 8) and nonsustained VT in 50% (n = 6). The mean PVC burden was 5.1% ± 6.8%, but only 2 patients had a PVC burden >10%. No patients had sustained VAs.

HYBRID PET/MRI. The dietary and fasting preparation was successfully completed by 11 of 12 patients, whereas 1 patient completed the dietary preparation and fasted 4 hours before the study. The mean fasting blood glucose before the scan was 100 ± 14 mg/dL. The patient who fasted for 4 hours had a fasting blood glucose of 86 mg/dL.

FIGURE 2 Pulsed-Wave Tissue Doppler, Holter, and Hybrid Positron Emission



Tomography/magnetic resonance imaging of a 58-year-old female with bileaflet mitral valve prolapse with mild mitral regurgitation and intermittent dizziness. **(A)** Transthoracic echocardiography–derived pulsed-wave tissue Doppler of the posterolateral mitral annulus (apical long-axis view), with associated Pickelhaube spike (26 cm/s). **(B)** Nonsustained ventricular tachycardia. The **red arrow** indicates peak tissue Doppler velocity. **(C to F)** f concordant fluorine 18–labeled fluorodeoxyglucose (FDG) uptake that colocalizes with late gadolinium enhancement (LGE). The **white arrowheads** indicate areas of either LGE or FDG uptake, respectively.

^{18}F-FDG uptake was present in 83% (n = 10) of the patients (Table 2). The ^{18}F-FDG uptake was localized to the papillary muscles and/or the inferolateral and basal inferior segments of the LV in 60% of patients (n = 6), whereas the remaining 40% (n = 4) exhibited a multifocal pattern. There were no cases suggestive of physiological (failed myocardial suppression) ^{18}F-FDG uptake. The mean SUVmax and TBRmax were 4.75 ± 3.12 and 3.06 ± 2.36, respectively.

Baseline cardiac MRI characteristics are described in Table 2. The mean left ventricular ejection fraction and indexed LV end-diastolic volume were 58.6% ± 5.8% and 85.2 ± 13.6 mL/m^2, respectively. Of the patients who were PET$^+$/MRI$^+$ (n = 9, 75%), fusion images showed concordance of myocardial ^{18}F-FDG uptake and LGE in all those patients (100%, n = 9 of 9). The mean percentage of LGE was 7.21% ± 5.13%. Native T1 values were abnormal in 58% (n = 7) of the patients, T2 values were abnormal in 25% (n = 3), and ECV was abnormal in 16% (n = 2).

DISCUSSION

In a cross-section of patients with degenerative MVP with only mild or moderate MR and ventricular ectopy, we detected focal or focal-on-diffuse uptake of FDG uptake (PET$^+$) in 83% (n = 10) and FDG uptake that was concordant with areas of LGE (PET$^+$/LGE$^+$) in three-quarters of the patients (75%, n = 9) (Figure 1). These findings suggest that chronic myocardial inflammation, as quantified by ^{18}F-FDG PET, may contribute to the pathogenesis of myocardial injury present in patients with the classic MVP, even with only mild or moderate MR. The prevalence and distribution of ^{18}F-FDG uptake and LGE is similar to what we previously have shown in a cohort of patients with severe MR who had been referred for consideration of mitral valve surgery.[10] The presence of ^{18}F-FDG, a surrogate marker of myocardial inflammation and marker of arrhythmic risk in other substrates, in this population of patients with less than severe MR might further explain why: 1) a significant percentage of

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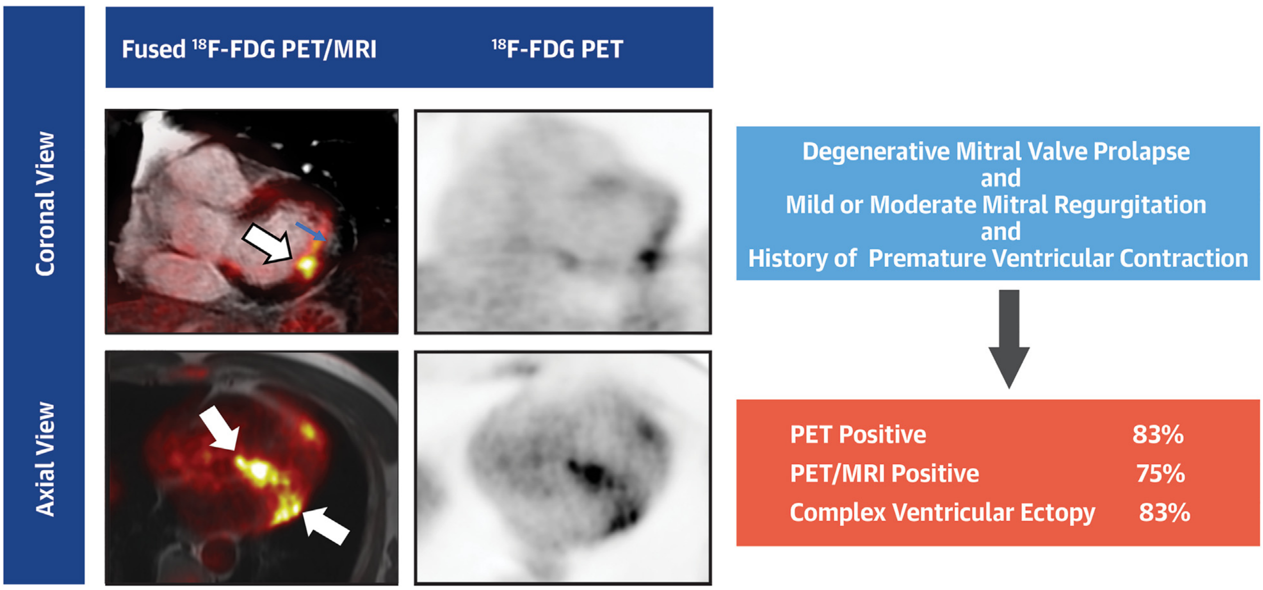
CENTRAL ILLUSTRATION Hybrid PET/MRI Findings and Ventricular Arrhythmia Complexity in Arrhythmic MVP Patients With Only Mild or Moderate MR



Miller MA, et al. J Am Coll Cardiol EP. 2023;9(8):1709-1716.

Focal fluorine 18-labeled fluorodeoxyglucose (^{18}F-FDG) in a patient with mitral valve prolapse and mild mitral regurgitation. Coronal and axial views show FDG uptake at the base of the heart **(white arrows)**, matching areas of late gadolinium enhancement **(blue arrow)**. MRI = magnetic resonance imaging; PET = positron emission tomography; PVC = premature ventricular contraction.

patients with only mild or moderate MR develop replacement fibrosis; 2) a majority of sudden deaths occur in patients with only mild or moderate MR; and 3) some MVP patients experience sudden death despite the absence of any evidence of replacement fibrosis.[1,3,5]

Elevated ECV, a surrogate of diffuse interstitial fibrosis, was present in only 2 patients, whereas evidence of inflammation and/or replacement fibrosis was present in 10 patients. Although it is a small number of patients overall, this "discrepancy" is consistent with other investigations that have shown that ECV is associated with the severity of the MR but not the prevalence/burden of replacement fibrosis or the etiology of the MR.[20] It is unlikely that these patients with preserved LV dimensions and only mild-moderate MR would have chronic LV volume overload, which is thought to be the dominant pathophysiological mechanism responsible for the development of diffuse interstitial fibrosis in patients with primary MR.[21] The mechanism for the development of elevated ECV in patients with MVP and less than severe MR remains to be determined, as does its contribution to the arrhythmic risk profile. Multisite interstitial fibrosis was a nearly universal finding in post-mortem study of MVP-related sudden death (malignant MVP), and diffuse interstitial fibrosis (as measured by ECV) was associated with an increased risk of out-of-hospital cardiac arrest in patients with ≥2 MRs, but imaging interstitial fibrosis in patients with only mild MR has not been extensively studied.[20,22]

MYOCARDIAL FIBROSIS, INFLAMMATION, AND VAs IN MVP. Although the precise pathophysiological mechanism leading to replacement fibrosis and inflammation in Barlow's MVP is incompletely understood, repetitive traction and acute stretch from the billowing leaflet on the papillary muscle and adjacent ventricular myocardium is hypothesized to induce the transformation of fibroblasts to myofibroblasts via expression of profibrotic cytokines and recruitment of inflammatory cells resulting in myocardial fibrosis.[3] This altered myocardial architecture creates a substrate in which re-entrant VAs (eg, VT/ventricular fibrillation) can form and propagate.[23] Additionally, activated fibroblasts can be proarrhythmic when coupled to adjacent cardiomyocytes because of electronic interaction that delays conduction and precipitate-triggered activity (eg, premature ventricular contractions).[24] Our findings suggest that patients with MVP have ongoing subclinical myocardial inflammation and injury independent of the degree of MR (**Figure 2**). Further investigation is needed to determine whether the myocardial traction-induced injury and inflammation can be predicted with other forms of imaging, and the time course over which it develops.[25]

STUDY LIMITATIONS. This study included a small number of patients and there was selection bias because all the patients had a history of premature ventricular contractions and were referred to a cardiac electrophysiologist. Therefore, these results cannot be extrapolated to patients without complex ventricular ectopy. The VA complexity and burden was based on ambulatory event monitors, which cannot accurately localize PVC origin. We do not know how long the patients had MVP; therefore, we cannot determine how long they had ongoing repetitive myocardial traction. We did not perform myocardial strain imaging, a marker of subclinical myocardial injury. ^{18}F-FDG uptake is not a direct measure of inflammation, and although standardized procedures were undertaken to minimize the possibility of a false-positive diagnosis, some structures (eg, papillary muscle) may be more prone to artifactual findings.[26] In this series of patients, all but 1 of the patients with FDG uptake in the papillary muscle also had corresponding matching LGE. We used a severity classification scheme for PVCs that has not been validated for use in patients with MVP. Our findings are only applicable to patients with Barlow's disease phenotype of degenerative mitral valve disease, and not to other forms (eg, fibroelastic deficiency) because they were not included in this series.[27]

CONCLUSIONS

Myocardial inflammation, concordant with myocardial scar, was detected in most patients with degenerative MVP, ventricular ectopy, and only mild or moderate MR (**Central Illustration**). Our findings suggest that myocardial inflammation and injury occurs before the development of significant MR and may partially explain the observation that a majority of MVP-related sudden deaths occur in patients with less than severe MR. Future larger studies with long-term follow-up are needed to determine how the presence of myocardial inflammation impacts the natural history of degenerative MVP, complexity of ventricular ectopy, and risk for sudden death.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This prospective observational pilot study of patients with arrhythmic MVP and only mild or moderate MR shows that myocardial inflammation and fibrosis occur in the absence of severe MR. Most of the patients had complex ventricular ectopy, although few had a significant burden of premature ventricular contractions. The proarrhythmic substrates of inflammation and fibrosis may contribute to the risk of sudden death in this particularly challenging patient population.

TRANSLATIONAL OUTLOOK: There is an unmet clinical need for risk stratification in arrhythmic MVP, particularly in those patients without an indication for valve intervention. These results will be used to perform a larger prospective assessment of the arrhythmic MVP phenotype across all spectrums of disease severity to determine which patients are most at risk for sustained VAs and what markers are predictive of that future arrhythmic risk.

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