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REVIEW

Arrhythmic mitral valve prolapse: a practical approach for asymptomatic patients

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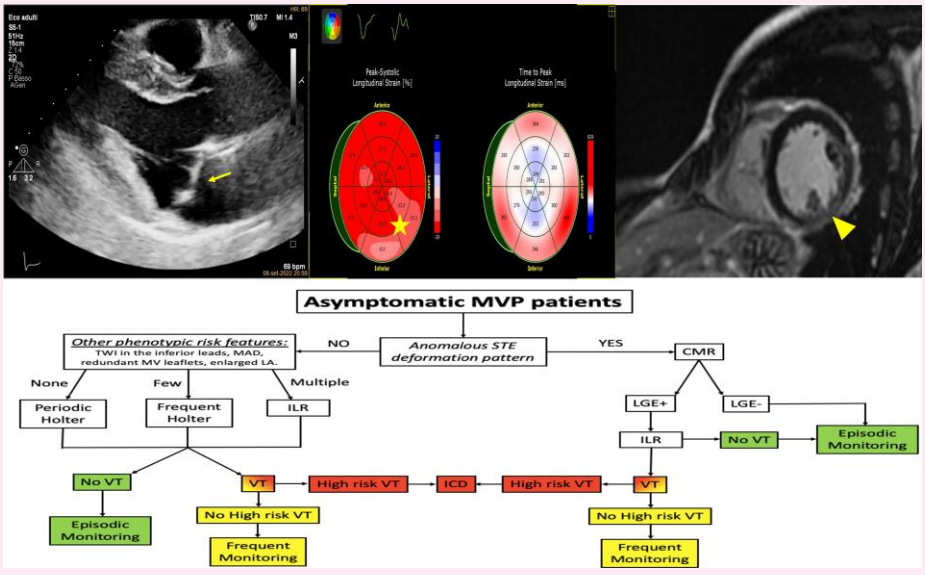
Mitral valve prolapse (MVP) is usually regarded as a benign condition though the proportion of patients with a life-threatening arrhythmic MVP form remains undefined. Recently, an experts' consensus statement on arrhythmic MVP has proposed approaches for risk stratification across the spectrum of clinical manifestation. However, sudden cardiac death may be the first presentation, making clinicians focused to early unmasking this subset of asymptomatic patients. Growing evidence on the role of cardiac imaging in the in-deep stratification pathway has emerged in the last decade. Pathology findings have suggested the fibrosis of papillary muscles and inferobasal left ventricular wall as the malignant hallmark. Cardiac magnetic resonance, while of limited availability, allows the identification of this arrhythmogenic substrate. Therefore, speckle-tracking echocardiography may be a gateway to prompt referring patients to further advanced imaging investigation. Our review aims to summarize the phenotypic features linked to the arrhythmic risk and to propose an image-based algorithm intended to help stratifying asymptomatic MVP patients.

Graphical Abstract



Keywords arrhythmic mitral valve prolapse • sudden cardiac death • speckle-tracking echocardiography

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Introduction

Mitral valve prolapse (MVP) is the most common valvular defect[1] affecting 2–3% of the general population[2,3] and is easily identified by echocardiography. Although the overall outcome of MVP in the absence of significant valvular regurgitation is widely considered benign, a subset of patients with this condition is at high risk for sudden cardiac death (SCD) and ventricular arrhythmias (VAs). The estimated incidence of SCD in unselected patients with MVP is <1%,[3–5] with an event rate in the community estimated at around 0.14 events/100 patients-year.[6] This apparently low incidence is not negligible due to the high prevalence of MVP. With MVP being the most plausible explanation in 11.7% of unexplained SCD cases, a recent meta-analysis found that MVP prevalence among all SCD cases was 1.9%.[6] Since SCD may be the first clinical manifestation, the risk stratification in these patients is a conundrum. To date, focusing efforts on the search for arrhythmic expression or the evidence of a silent malignant substrate is still debated. Numerous risk variables, such as female sex, bileaflet MVP, complicated VA, left ventricular (LV) dysfunction, myocardial fibrosis, and the presence of mitral annular disjunction (MAD), have been linked to SCD/VA in MVP patients.[7] Newly growing findings highlight the key role that cardiac imaging plays in the identification of patients at augmented risk of SCD/VA among the *mare magnum* of MVP carriers. With MAD as the most studied and recognizable feature, other morpho-functional anomalies of the mitral valve apparatus could be overlooked even if they are considered part of the arrhythmic MVP (aMVP) complex. Of note, changes in deformation pattern may be found by LV speckle-tracking echocardiography (STE) analysis, providing new insights into the understanding of mitral valve and LV myocardial relationship.[8] This review aims to address the whole spectrum of morphological features linked to aMVP and to suggest an imaging-based algorithm to help stratify asymptomatic MVP patients.

AMVP phenotypes and pathophysiological hypothesis

According to the most recent consensus document,[9] aMVP is defined by: (i) MVP with or without MAD and (ii) VA defined as frequent (if premature ventricular complex burden is >5%) or complex [ventricular tachycardia (VT) or ventricular fibrillation (VF)]. A correlation between mitral valvular complex abnormalities and arrhythmic outcomes being very hard to establish (e.g. it is not possible to design a trial to test the hypothesis that treating MVP reduces the incidence of arrhythmic events), a great amount of effort has been spent in recent years to identify patients at augmented risk deriving data by cohort observational studies. The identification of these phenotypical features plays a valuable role in the risk stratification process. Moreover, these data contributed for the most part to the identification of the pathophysiological process that causes arrhythmogenesis in patients with MVP.

Myxomatous disease

As endorsed by the latest consensus paper by the European Heart Rhythm Association (EHRA) on aMVP, two distinct phenotypes of this entity are recognized.[9] The first one is severe degenerative mitral regurgitation (MR), an entity whose prognostic significance and therapeutic implications are renowned and are beyond the scope of this review.[10] The second more erratic entity is defined as severe myxomatous MVP (independent of MR). This definition encompasses marked leaflet redundancy, excessive leaflet length and thickness, and bileaflet prolapse (in the presence or absence of MAD). Even if the association between floppy valve (and MAD) and SCD was reported in some seminal case series,[11] the first insights from a large cohort came only in recent years. In 2013, Sriram *et al.*, from a cohort of over 1000 patients with cardiac arrest, identified in a subset of patients without any other plausible cause a significant incidence of bileaflet MVP.[12] Similarly, in a large cohort of implantable cardioverter-defibrillator (ICD) carriers who survived VF without any structural or electrical abnormality other than MVP, severe MVP with MAD was detected in 96% of subjects.[13] Severe MVP with MAD confirmed its independent association with arrhythmic outcomes in a large cohort of MVP patients assessed with Holter monitoring.[14] Moreover, bileaflet MVP, abnormal mitral annulus diameters, and leaflet curling resulted in a correlation with the presence of LV fibrosis assessed by cardiac magnetic resonance (CMR) imaging, the most probable arrhythmogenic substrate in aMV.[15,16] All these data converged in the most accepted physiopathological mechanism of arrhythmogenesis in aMVP according to which these MVP features cause an abnormal stretching of underlying ventricular structures causing fibrous degeneration of myocardial tissue. Risk stratification based on these morphological features is appealing because it is performed with a standard echocardiographic examination but surely suffers from its qualitative nature and lack of standardization. A recent meta-analysis tried to overcome the limits of the available data by pooling several large cohort studies. That showed a significantly higher incidence of bileaflet prolapse in aMVP compared with MVP and reported a significantly longer anterior leaflet in aMVP subjects.[17]

Mitral annulus disjunction

MAD is the most recognizable morphological feature of aMVP and the one with the greatest amount of evidence supporting its prognostic role. Its presence has been considered mandatory to define aMVP for many years; now, it is becoming clearer that this relationship is not as straightforward as it was considered. The most widely accepted definition of MAD is a systolic separation between the ventricular wall and the mitral annulus supporting the posterior mitral leaflet (PML),[18] with a quantifiable gap between these structures during systolic leaflets doming. Due to this anatomical feature, the mitral annulus loses its mechanical function, but the electric isolation between atrial and ventricular tissue is maintained.[16,19] MAD is usually described at the fibromuscular posterior mitral annulus due to the presence of mitro-aortic *fibrosa* in continuity with the anterior leaflet. It is easily identifiable in long-axis view with transthoracic echocardiography or CMR (*Figure 1*).[20–23] During systole, the posterior mitral annulus shows a brisk upward motion, which is called 'curling' and is studied frame-by-frame to detect the precise location of the leaflet insertion. The lower limit of MAD is therefore defined at the level of the LV myocardium, whereas the higher limit is established at the level of PML insertion on the annulus/left atrial wall. First described by the anatomist Henle in 1876 the first clinical correlation of MAD appeared in 1981 with the case report of a 45-year-old physician with MAD who suffered cardiac arrest.[24] Since then, several observational reports tried to highlight the prognostic role of MAD in MVP with significant disagreement in terms of results. An autoptic case series[25] and an echocardiographic observational study[20] reported MAD as a benign entity with correlations only with an augmented incidence of MVP. Conversely, a pivotal study about aMVP found that MAD is far more frequent in patients with LV myocardial fibrosis suggesting the key role of this morphologic feature in myocardial stretching.[16] Moreover, an observational study on patients with a history of MVP who experienced SCD showed that severe MVP and MAD were reported in most of the cases.[13] The first study systematically analysing the arrhythmic outcome in a large cohort of MVP patients revealed that severe VAs are rare and that MAD is the principal feature of the aMVP.[14] To focus on the relative prognostic role of MAD, in the same cohort long-term outcomes were analysed comparing MVP patients with and without MAD. The 10-year risk of death was not significantly higher in patients with MAD; however, a significantly augmented risk of arrhythmic events was reported (VT

Table 1 Prevalence of mitral annular disjunction

Study	Year	Population	Prevalence of MAD, *n/N* (%)
TTE			
Carmo *et al.*[22]	2010	Myxomatous mitral valve prolapse	21/38 (55)
Lee *et al.*[27]	2017	Mitral valve prolapse	42/156 (27)
Konda *et al.*[20]	2017	Patients referred for TTE	125/1439 (9)
Mantegazza *et al.*[28]	2019	Mitral valve prolapse, severe MR	103/979 (16)
Torras *et al.*[29]	2019	Mitral valve prolapse	22/101 (22)
Essayagh *et al.*[19]	2021	Mitral valve prolapse	186/596 (31)
Essayagh *et al.*[30]	2021	Mitral valve prolapse and severe MR undergoing repair	27/61 (44)
CMR			
Christiansen *et al.*[31]	2010	Mitral valve prolapse undergoing CMR	18/31 (58)
Perazzolo Marra *et al.*[16]	2016	Arrhythmic myxomatous mitral valve prolapse	37/52 (71)
Essayagh *et al.*[32]	2019	Mitral valve prolapse	31/89 (35)
Zugwitz *et al.*[33]	2022	UK Biobank imaging study participants	1990/2607 (76)
Figliozzi *et al.*[26]	2023	Mitral valve prolapse	321/474 (68)

TTE, transthoracic echocardiography.

occurrence, VT or disabling PVC ablation, ICD implantation, SCD).[19] A recent observational study on a very large cohort of patients with MVP assessed with CMR contributed to reconsidering the prognostic role of MAD. Over a median follow-up of 3.3 years, MAD was not associated with a composite arrhythmic outcome (sustained VT, SCD, unexplained syncope).[26] Inhomogeneity in the definition of MAD adopted in different studies could explain these apparently inconsistent results. The prevalence of MAD in MVP patient's cohort shows significant variations according to the examined studies (*Table 1*) with a significantly higher prevalence when CMR was the imaging modality performed.

Indeed, the exact relationship between MAD and other MVP characteristics remains uncertain and MAD has been interpreted as preceding MVP diagnosis,[11] unrelated to MVP,[20,34] or as a consequence of myxomatous MVP itself.[21,35] Moreover, studies about MAD outside the context of MVP contributed to the uncertainty in dealing with this morphological entity. Two observational studies on Japanese subjects reported a significant prevalence of MAD in structurally normal hearts (8.7% with echocardiography and 96% with cardiac computerized tomography) with a higher prevalence in patients with MV.[20,36] A recent analysis from the Biobank Imaging Study reported disjunction in 76% of the 2607 participants, more frequently at the anterior and the inferior ventricular wall. Inferolateral disjunction, which is considered clinically relevant due to the spatial relationship with myocardial fibrosis, was found only in 5% of cases. MVP, billowing, and curling were associated with disjunction, especially with inferolateral MAD.[33] Apparently in contrast with this interpretation, Dejgaard *et al.*[34] in 2018 reported arrhythmic outcomes in a cohort of 116 MAD carriers with or without MVP. Patients with severe arrhythmic events (aborted SCD and sustained VT) presented a higher prevalence of LGE strengthening the link among MAD, LV fibrosis, and arrhythmias. Surprisingly, a fifth of patients did not present MVP, and prolapse was not associated with arrhythmias. The authors concluded that this evidence suggests that MAD can exist and portends arrhythmic events even outside the aMVP setting. In this complex scenario, other authors identify the source of the unintelligibility of MAD in the misconception of its morphological features. The authors state that the definition of MAD as a dynamic systolic entity is intrinsically inconsistent and that 'real' MAD must be identifiable in systole and diastole, too. Unfortunately, echocardiography does not have the spatial resolution to distinguish MAD from 'pseudo-MAD' (only a visual aspect of the redundant PML that slides on the atrial wall in systole), and CMR should be employed to study the 'atrialized' insertion of MV leaflet in diastole.[37] Prognostic data considering this suggested dichotomy of MAD are not yet available.

LV myocardial fibrosis

Myocardial fibrosis is well recognized as a substrate for arrhythmogenesis in different clinical settings such as coronary artery disease, inflammatory cardiac disease, and arrhythmogenic cardiomyopathies. The presence of LV fibrosis and its relationship with clinical outcomes is an active matter of research in mitral valve disease too. In a seminal study on MVP diagnostic characterization at CMR, a significantly higher prevalence of LGE at the papillary muscles was reported in patients with arrhythmic events.[38] Similarly, myocardial fibrosis assessed with LGE in patients with MR showed a higher prevalence in MVP patients with respect to other valvular morphologies.[39] Moving from this point, in one of the first systematic studies on aMVP, SCD victims underwent histological examination to identify the potential origin of arrhythmic events. Significant fibrosis at the level of papillary muscles was identified in all the patients, and 88% of them showed inferobasal fibrosis. Concurrently, in living patients with severe arrhythmias, LV late enhancement was identified by contrast-enhanced CMR in 93% of cases with a regional distribution overlapping the histopathology findings in SCD cases.[15] In a subsequent work from the same group, LV fibrosis in patients with MVP resulted in being associated with severe myxomatous disease and MAD reinforcing the link between abnormal anatomy and arrhythmic outcomes in MVP.[16] Another observational study on 89 patients with MVP from myxomatous disease or fibroelastic deficiency showed a higher prevalence of myxomatous disease and MAD in patients with LGE at CMR.[32] LV fibrosis is frequently identified in patients with MR with a gradient from mild to severe disease, and it is interpreted as the result of maladaptive LV remodelling.[40] With the aim of identifying the additive role of LGE at CMR in patients without significant MR, a recent international multi-centric observational study analysed the arrhythmic outcomes of patients with MVP without more than mild regurgitation. In this cohort of 474 patients, LGE presence and extent (but not MAD) were associated with clinical outcomes (sustained VT, SCD, unexplained syncope).[26]

LV strain analysis

STE among other advanced echocardiographic applications has been developed to overcome the limitations of standard echocardiography in the identification of subtle myocardial dysfunction. Its diagnostic performance in specific settings has raised the level of recommendations for its systematic application (e.g. cardio-oncology, cardiac amyloidosis).[41–43] The higher sensitivity of STE compared with standard echocardiography seems related to the capacity of early identification of myocardial damage.[44] This hypothesis has been tested in many clinical settings in which STE showed a good correlation with histological assessment of cardiac fibrosis or LGE at CMR.[45–51] Moving from these perspectives, the application of STE in identifying subtle myocardial damage or early myocardial fibrosis in MVP patients appears reasonable. In this setting, different deformational patterns could be identified (*Figure 2*), and abnormalities in

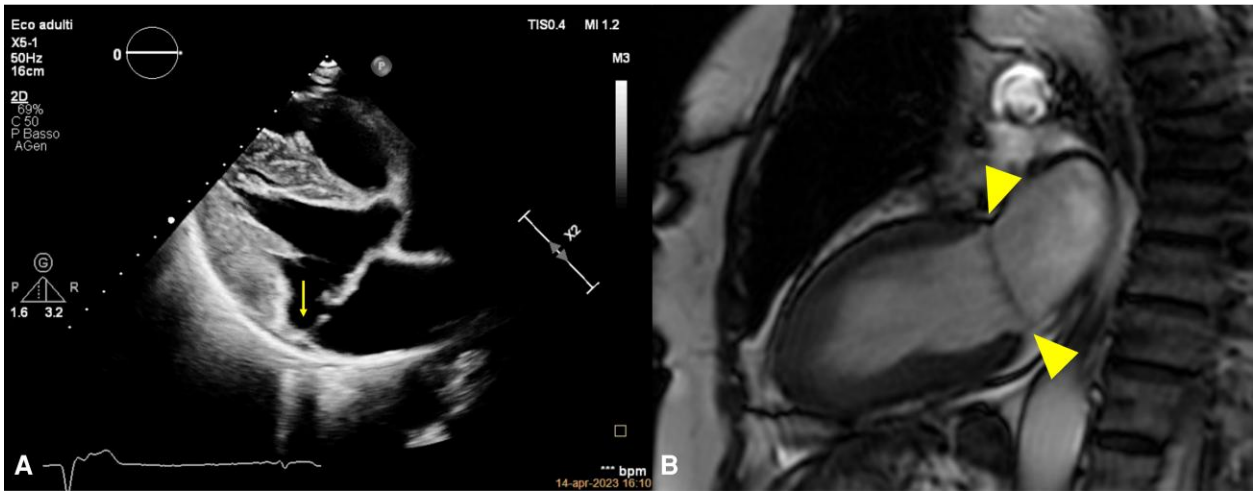

Figure 1 Parasternal long-axis echocardiographic view displaying a significant MAD of 12 mm (*A*, arrow). CMR demonstrating bileaflet MAD (*B*, triangles).

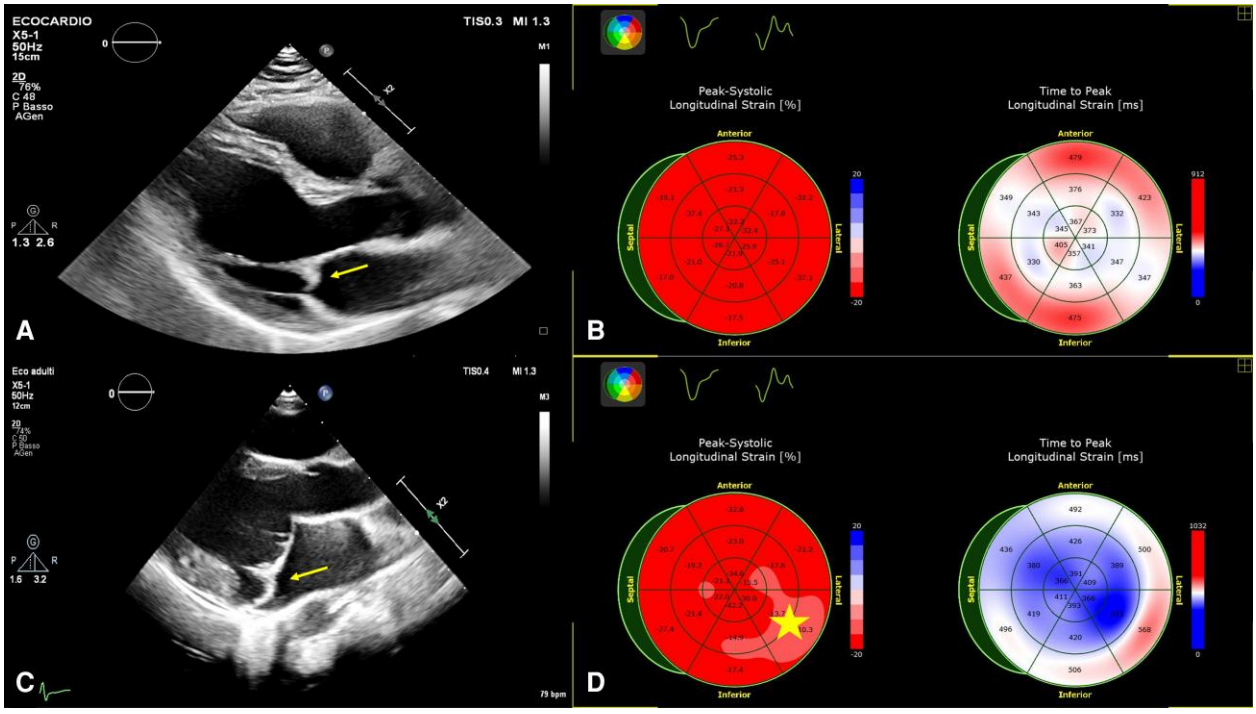

Figure 2 PML prolapse (*A*, arrow) and normal STE analysis on 2D echocardiography (*B*). Conversely, PML prolapse (*C*, arrow) and anomalous LV myocardial deformation pattern (*D*, star).

LV strain and strain-derived parameters showed a correlation with arrhythmic outcomes. Mechanical dispersion (a STE-derived parameter) has been employed to study patients with and without arrhythmic events compared with controls. Comparing cohorts with similar demographics, LV ejection fraction (LVEF) and global longitudinal strain, mechanical dispersion resulted in being independently correlated to arrhythmic events.[52] Moreover, a recent cohort study comparing SCD survivors with MVP, MVP patients with a high burden of PVC and patients without an arrhythmic history showed a significant gradient in the comparisons between deformational patterns.[53] A recent study on MVP patients compared peak segmental longitudinal strain (PSS) and myocardial work index (MWI) in subjects with and without arrhythmias during follow-up and in control subjects. PSS and segmental MWI for basal lateral, mid-lateral, mid-posterior, and mid-inferior segments were the

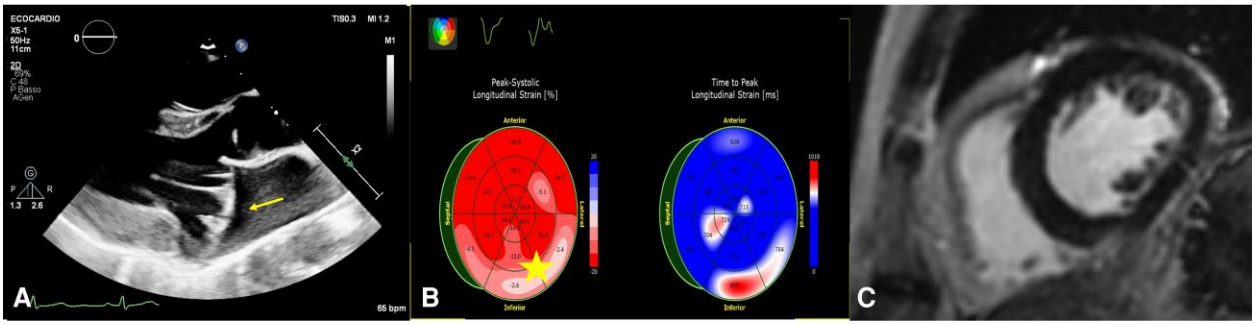

Figure 3 Bileaflet MVP on 2D echocardiography (*A*, arrow). The LV myocardial STE analysis showing an anomalous pattern (*B*, star). CMR was unremarkable (*C*).

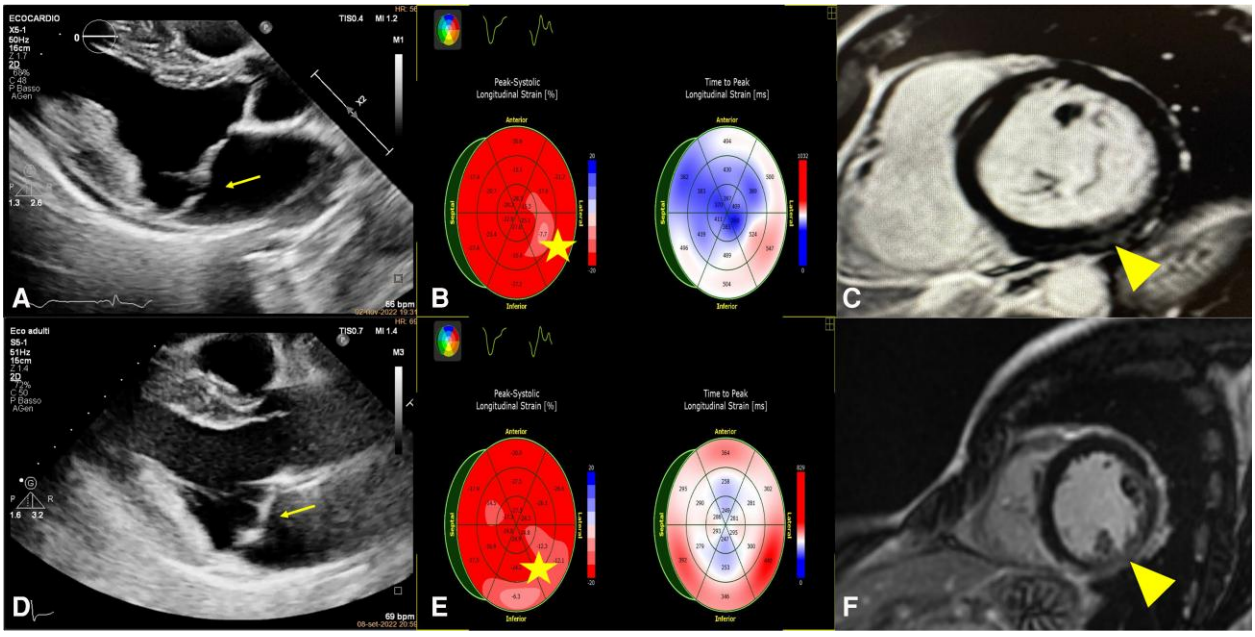

Figure 4 Parasternal long-axis echocardiographic view showing a PML prolapse and MAD (*A*, arrow), combined with slightly abnormal STE-derived LV deformation pattern (*B*, star). Parasternal long-axis echocardiographic view demonstrating an anterior mitral leaflet prolapse with tissue redundancy and hypoplastic PML (*D*, arrow), combined with overt anomalous LV longitudinal strain (*E*, star). On both CMR, the presence of LGE at the level of LV inferolateral wall was visible (*C*–*F*, triangle).

accurate predictors of complex VAs showing good correlation with the most frequent locations of myocardial fibrosis at CMR.[54] Similarly, another study on 113 MVP subjects assessed with CMR and STE reported that patients with basal–midventricular inferior–lateral wall and papillary muscles LGE showed greater MR, prolapse, and superior papillary muscle displacement with basal curling and more impaired inferior–posterior basal strain than those without fibrosis. A specific strain pattern with a double peak (pre-telesystolic and post-telesystolic) in the inferolateral wall was identified in patients with fibrosis and showed a good correlation with arrhythmic events.[55] It is noteworthy that STE abnormalities in MVP patients do not always imply underlying myocardial fibrosis. Indeed, the dynamic interplay between the mitral apparatus and ventricular wall may alter the deformation pattern due to myocardial stretching (*Figure 3*). The first observational evidence of this dynamic effect of MVP was derived in patients with severe myxomatous disease, where STE demonstrated an association with a weaker contraction in the LV inferolateral segments.[56]

Clinical cases

Case 1

A 53-year-old male, without notable cardiovascular history, suddenly collapsed at home without any preceding suspected symptoms. The mobile emergency response team administered urgent advanced life support for him, detecting VF, which required two defibrillations before

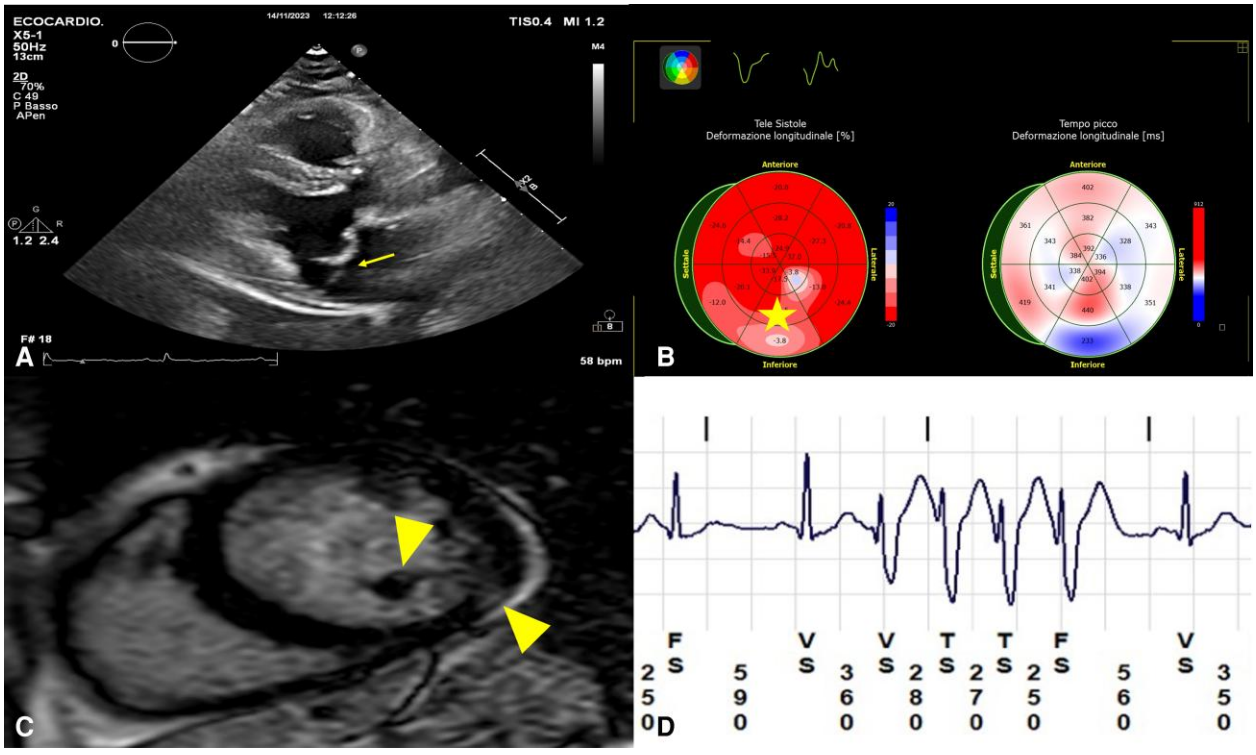

Figure 5 Parasternal long-axis echocardiographic view showing a PML prolapse and MAD (*A*, arrow). LV STE analysis displaying an anomalous LV deformation pattern (*B*, star). On CMR, LGE was recognizable at the level of LV inferobasal wall and papillary muscle (*C*, triangle). Single episode of non-sustained monomorphic VT diagnosed by long-time monitoring with ILR (*D*).

returning to sinus rhythm. The patient was then sent to the hospital for additional investigations upon resuscitation and admitted to the intensive care unit while unconscious and on mechanical ventilation. The surface electrocardiogram (ECG) was unremarkable. Echocardiography showed an MVP of the PML with MAD and mild regurgitation (*Figure 4A*). The LV was hyperkinetic. Some paroxysms of anterior ST-segment elevation were noted throughout the ECG monitoring. A coronary angiogram revealed an isolated soft plaque in the proximal anterior descending artery, with severe stenosis at 80–90%, treated by angioplasty and placement of a drug-eluting stent. Cardiac troponin I was slightly above the normal range, raising doubts concerning the ischaemic aetiology of the life-threatening arrhythmia. After weaning from mechanical ventilation, CMR excluded oedema on T2-weighted sequences. Late gadolinium enhancement (LGE) was present in the mid segment of the inferolateral wall, endorsing the replacement of myocardial fibrosis (*Figure 4C*). A regional agreement with LV STE analysis was observed (*Figure 4B*). Finally, we performed an ICD implantation as secondary prophylaxis.

Case 2

A 37-year-old previously healthy male collapsed at work, witnessed by a colleague who quickly started bystander cardiopulmonary resuscitation. VF was diagnosed on arrival of the medical team. A direct current shock was delivered resulting in sinus rhythm and return of spontaneous circulation, before transferring the patient to the intensive care unit. Surface ECG was unremarkable. Transthoracic echocardiography revealed an elongated sail-like anterior mitral leaflet and a motionless hypoplastic PML, with preserved LV systolic function (*Figure 4D*). LV STE analysis showed the presence of segmental longitudinal dysfunction (*Figure 4E*). Coronary angiography did not reveal any stenoses of the coronary vessels. Subsequent CMR disclosed MAD. On T2-weighted sequences, there was no evidence of cardiac oedema. Late gadolinium sequences revealed overt non-ischaemic enhancement of the LV basal and mid inferolateral wall (*Figure 4F*), consistent with the STE-derived anomalous myocardial deformation pattern. A subcutaneous automatic defibrillator was implanted for secondary prevention of SCD.

These two anecdotal clinical cases show the phenotypic variability of the mitral valve apparatus in patients with an arrhythmogenic substrate. Nonetheless, both exhibited abnormal LV longitudinal strain, highlighting the useful role of LV STE analysis in unmasking myocardial fibrosis due to prolapsed leaflet stretching better than a single mitral valve morphological feature.

Case 3

An asymptomatic 29-year-old woman presented to our echo lab for regular follow-up of a known MVP. A diagnosis of PML prolapse with MAD and trivial regurgitation was confirmed by echocardiography (*Figure 5A*). The LVEF was normal. Conversely, LV STE analysis displayed an anomalous myocardial deformation pattern (*Figure 5B*), worthy of further investigations. Surface ECG was unremarkable. Twenty-four-hour Holter monitoring showed isolated premature ventricular complexes. CMR revealed mild LGE in the LV basal inferolateral myocardium and papillary muscle (*Figure 5C*). To better stratify her arrhythmic risk, the implantation of an implantable loop recorder (ILR) was performed, leading to the diagnosis of one episode of non-sustained monomorphic VT 5 months later (*Figure 5D*). This arrhythmia was judged to be a non-high risk VT. Therefore, the patient was kept under monitoring.

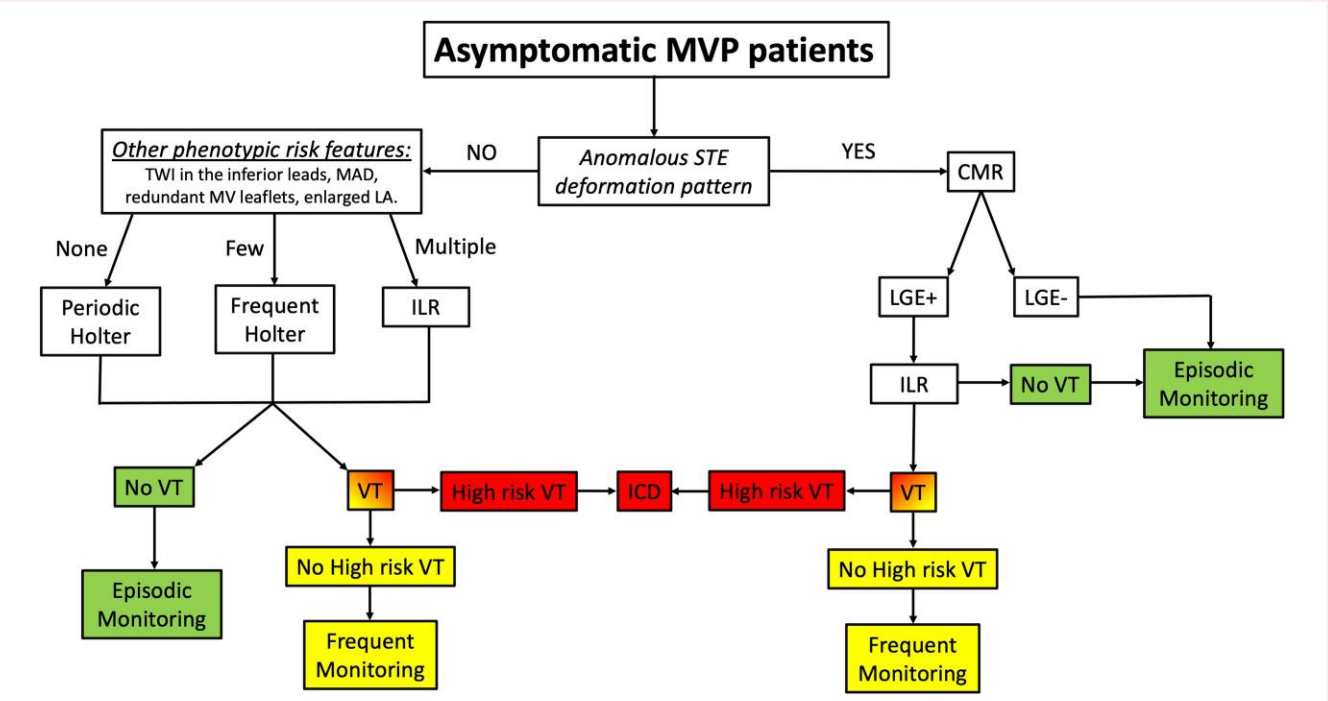

Figure 6 Image-based algorithm in asymptomatic MVP patients suggesting STE as a useful tool for risk stratification. On the right, abnormal STE addresses for further investigation by CMR; on the left, in the absence of anomalous myocardial deformation pattern, other phenotypic risk features may trigger the intensity of searching for an arrhythmic expression. TWI, T-wave inversion; LA, left atrium.

This clinical case underlines the limitations of a symptom-based strategy to define the arrhythmic risk and the utility of advanced imaging techniques to search for an arrhythmogenic substrate in selected asymptomatic MVP patients.

Risk stratification: proposal of an image-based algorithm in asymptomatic patients

Risk stratification in aMVP patients is challenging due to the lack of prospective outcome data. Recently, an European experts' consensus statement on aMVP has proposed approaches for risk stratification across the spectrum of clinical manifestation,[9] also aiming to guide future clinical trials and collaborative research in alignment with an American expert panel.[57] While secondary prevention ICD is indicated by guidelines in aMVP patients with aborted cardiac arrest,[58] how to manage the other patients at risk of serious arrhythmias is still puzzling. SCD may be the first clinical scenario, making symptoms of partial predictive value. Phenotypic risk peculiarities may trigger the intensity of searching for an arrhythmogenic substrate in asymptomatic patients. To date, which anatomical feature or set of anatomical features is responsible for the increased arrhythmic risk is still controversial. Nevertheless, promising pathology evidence supports the fibrosis of the papillary muscles and inferobasal LV wall due to the myocardial stretch of the prolapsing leaflets as the malignant substrate.[15] CMR allows the *in vivo* identification of this structural hallmark.[38,39,59] However, the availability of advanced imaging methods is limited and varies patchily, making the patient's selection mandatory. Our review underscores the value of STE analysis in searching for LV myocardial fibrosis. Accordingly, we would like to propose a new image-based algorithm to integrate the EHRA risk stratification scheme for the management of asymptomatic MVP patients (*Figure 6*). Based on our proposal, finding anomalous LV longitudinal strain patterns at routine echocardiography should lead to further investigation by CMR. Conversely, excluding abnormal LV myocardial deformation would make it possible to postpone the search for the malignant substrate by advanced imaging. ILR use may appear reasonable in LGE+ patients or in case of multiple anatomical features as an option to look for silent VAs. Primary prevention implantation of ICD should be a recommended indication in patients presenting high-risk VAs as suggested by the EHRA committee. Catheter ablation of papillary muscle premature ventricular contractions could be a possible treatment alternative.[60,61]

Conclusions

Arrhythmic patient with MVP is still an intricate conundrum. Prevention of SCD is challenging, and squaring the circle is an ongoing effort by the scientific community. Our review focused on the main morphological risk features, suggesting a new image-based algorithm to help clinicians stratify the asymptomatic patients. To date, CMR is a promising non-invasive tool for searching a hallmark of the malignant substrate, limited by patchy availability. Waiting for the outcome evidence, STE analysis may be a useful tool to refer patients to further advanced imaging techniques.

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Data availability

Not applicable.

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