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Arrhythmic mitral valve prolapse and mitral annular disjunction: pathophysiology, risk stratification, and management

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Abstract

Mitral valve prolapse (MVP) is the most frequent valve condition but remains a conundrum in many aspects, particularly in regard to the existence and frequency of an arrhythmic form (AMVP) and its link to sudden cardiac death. Furthermore, the presence, frequency, and significance of the anatomic functional feature called mitral annular disjunction (MAD) have remained widely disputed. Recent case series and cohorts have shattered the concept that MVP is most generally benign and have emphasized the various phenotypes associated with clinically significant ventricular arrhythmias, including AMVP. The definition, evaluation, follow-up, and management of AMVP represent the focus of the present review, strengthened by recent coherent studies defining an arrhythmic MVP phenotypic that would affect a small subset of patients with MVP at concentrated high risk. The role of MAD in this context is of particular importance, and this review highlights the characteristics of AMVP phenotypes and MAD, their clinical, multimodality imaging, and rhythmic evaluation. These seminal facts lead to proposing a risk stratification clinical pathway with consideration of medical, rhythmologic, and surgical management and have been objects of recent expert consensus statements and of proposals for new research directions.

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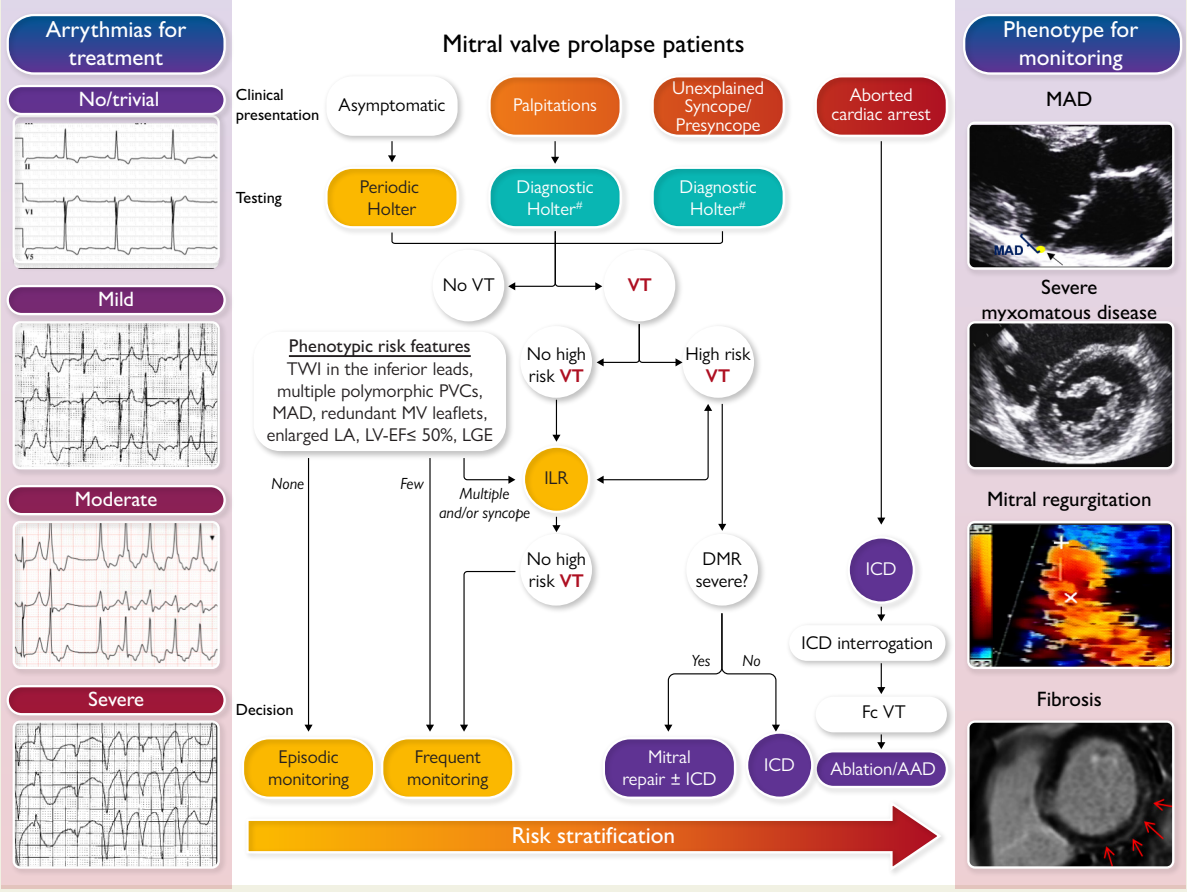
Graphical Abstract



Pathophysiology, risk stratification and management of arrhythmic mitral valve prolapse and mitral annular disjunction. (Left panel, from top-to-bottom) No/trivial, mild, moderate, and severe ventricular arrhythmia. (Middle panel) Risk stratification aiming at assessing the risk of ventricular arrhythmias and sudden cardiac death in patients with mitral valve prolapse, involving two phases based on the clinical and imaging context and the uncovered arrhythmia. In the absence of ventricular tachycardia, phenotypic risk features will trigger the intensity of screening for arrhythmia. Green boxes indicate green heart consensus statements, and yellow boxes indicate yellow heart consensus statements. High risk = sustained ventricular tachycardia, polymorphic non-sustained ventricular tachycardia, fast (>180 b.p.m.) non-sustained ventricular tachycardia, ventricular tachycardia/non-sustained ventricular tachycardia resulting in syncope. (Right panel, from top to bottom) The arrhythmic mitral valve prolapse imaging phenotype with bileaflet mitral valve prolapse and mitral annular disjunction, leaflet redundancy, mitral regurgitation severity, and late gadolinium enhancement. AAD, anti-arrhythmic drug; DMR, degenerative mitral regurgitation; ICD, implantable cardioverter-defibrillator; LA, left atrium; LGE, late gadolinium enhancement; LV-EF, left ventricular ejection fraction; MAD, mitral annular disjunction; MV, mitral valve; PVC, premature ventricular complex; TWI, T-wave inversion; VT, ventricular tachycardia. #Additional electrocardiogram monitoring method may be used such as loop recorders. Modified from Essayagh *et al.* and Sabbag *et al.*[36,44]

Keywords Mitral valve prolapse • Ventricular arrhythmia • Ventricular tachycardia • Ventricular fibrillation • Syncope • Sudden cardiac death

The conundrum of mitral valve prolapse and sudden cardiac death

Mitral valve prolapse (MVP) is the most frequent valve condition in Western countries, with a prevalence between 0.6% and 2.4% of the population.[1–3] Since its description based on auscultatory findings, reports on outcome have alternated between descriptions of few complications[4] and case reports of sudden cardiac deaths (SCDs)[5] unexplained by any other obvious conditions, leaving clinicians in a conundrum. This uncertainty is amplified by several factors that hinder obtaining definitive and informative data. First, SCD is fortunately a rare clinical event, which makes it a difficult endpoint to analyze in clinical cohorts.[6] Furthermore, once SCD has occurred, it is challenging to define precisely the cause/mechanisms. Second, MVP is a condition with considerable heterogeneity, affecting the severity of the myxomatous degeneration, the severity of the prolapse, the severity of degenerative mitral regurgitation (DMR), and the magnitude of ventricular/atrial responses to MVP/DMR, among other factors. Third, MVP and DMR are not static and lesions progress over time[7,8] with variable progression of DMR severity[9] but both severity and progression are seldomly

quantified precisely. Fourth, evanescent and non-specific manifestations make clinical diagnosis of the condition and its complications at best tentative. Thus, it is not surprising that diagnosis, monitoring, and management of ventricular arrhythmias associated with MVP are barely mentioned in clinical guidelines for the management of valve diseases.[10,11]

Morphologically, there are also important sources of confusion. The demonstration of the saddle shape of the mitral annulus[12,13] underscored the many previous inappropriate MVP diagnoses in the echocardiographic four-chamber views. Thus, the integrity of older series that suggested potential association between MVP and SCD[14] was profoundly questioned. Uncertainty also regards mitral annular disjunction (MAD), mentioned alternatively as strongly associated with MVP[15] or as a normal variant of the mitral annulus.[16] Thus, its potential clinical impact has long been forgotten.[17]

Due to these multiple sources of uncertainty, the issue of SCD in MVP remained undefined and was approached from a different angle, using population-based cohorts whereby MVP heterogeneity can be accounted at baseline. These population-based data strongly suggested that MVP without "significant" DMR or left ventricular (LV) dysfunction is a benign condition,[3,18,19] an assertion confirmed in large cohorts.[20] Hence, with multiple data sources affirming the benign outcome of the large group of MVP with little DMR enjoying survival after diagnosis equivalent to that of the general population, is the question of SCD in patients with MVP overblown and should it be marginalized as reflecting random events? It is certainly not, because a large group of patients with a benign prognosis may conceal a small subset of patients at notable risk for SCD. Indeed, case series of SCD in patients with MVP,[14,21] albeit small, have renewed the interest in investigating SCD with MVP.[22,23] Therefore, new issues were raised regarding the risks incurred by patients with MVP and their evaluation, follow-up, and management, which form the background of the present review.

Illustrative cases

Case #1: A 72-year-old active and asymptomatic male, with past medical history significant for prior tobacco use, hypertension, and hyperlipidemia, presented for follow-up of mitral regurgitation (MR). Three years earlier, he had atypical chest pain and coronary angiography showed minor coronary abnormality with mild-to-moderate MR. Examination showed a 3/6 systolic murmur and Doppler echocardiography demonstrated a small flail segment of the posterior leaflet (*Figure 1*, upper row), with DMR graded moderate to severe, quantified as effective regurgitant orifice 0.30 cm^2, with regurgitant volume 84 mL/beat, (*Figure 1*, middle row) with ejection fraction 64% and mildly increased LV size. Exercise testing showed peak oxygen consumption at 107% of expected. However, at peak exercise, a short burst of ventricular tachycardia (VT) was noted (*Figure 1*, lower-row left). The patient was not interested in considering mitral surgery and follow-up at 6 months showed no change, with similar refusal of considering surgery. A month later, the patient became unresponsive at work and was found to be in ventricular fibrillation necessitating two shocks before return to sinus rhythm. The patient was neurologically intact with unchanged physical examination. Coronary angiogram (*Figure 1*, lower-row right) reported 40% middle left anterior descending and 60% marginal branch obstruction. The patient underwent mitral repair with coronary bypass grafting to both arteries, followed by implantable cardioverter-defibrillator (ICD) implantation. During follow-up years, no ICD discharges were noted.

Case #2: A 26-year-old active female had a history starting at age 17 of pre-syncopal episodes resolving promptly, with few episodes of complete blackouts and without family history of sudden death. A few months prior, she started working as nursing aid in a hospital. She suddenly collapsed at work, with the code team detecting ventricular fibrillation, which required eight defibrillations before returning to sinus rhythm. The patient was neurologically intact, coronary angiography negative, and echocardiography showed bileaflet MVP with notable MAD (*Figure 2*, upper-row) with trivial DMR (*Figure 2*, middle-row right) and normal left and right ventricular function (*Figure 2*, lower-row). Monitoring showed numerous episodes of VT (*Figure 2*, middle-row left). Genetic panel for arrhythmic myopathy was negative. Implantable cardioverter-defibrillator implantation was followed by multiple shocks for ventricular fibrillation initiated by single ventricular extra-systole. After two ablations of extra-systole foci, there were no recurrences of ventricular fibrillation episodes.

These two cases underscore from different perspectives the potential association and uncertainties of MVP with the ultimate complication of SCD.[24]

The benign or malignant mitral valve prolapse?

The literature on MVP has been peppered with case reports[5,25–28] of patients who suffered occurrence of SCD and were found to be carriers of isolated MVP.[29–34] While it is tempting to presume a link between MVP and SCD, establishing scientific causality is much more uncertain and demanding[27] because MVP is often unknown before SCD, the event is exceptionally monitored,[24] autopsy cannot ascertain arrhythmic events, other causes of arrhythmic SCD (e.g. long QT) are often not ruled out, and it is not possible to collect the ultimate proof of causality, i.e. a clinical trial eliminating the cause (MVP) and suppressing the consequence (SCD risk).

In view of these methodological difficulties, the issue was shifted to that of MVP-related potential excess mortality (linked to SCD?) and potential excess representation among SCD cases. The relevant literature is summarized *Table 1*.

Mitral valve prolapse cohorts (*Table 1*, top rows cohorts) population based (Framingham and Olmsted) clearly established[3,19] that MVP with no/trivial DMR, as a group, has normal life expectancy. While these groups had modest sample sizes, large cohorts confirmed the benign outcomes of MVP with no/mild DMR[20] or bileaflet.[35] This sense of benign outcomes was reinforced by autopsy series MVP specific (*Table 1*, autopsy rows) and non-MVP specific (see Supplementary data online, *Table S1*) that on average failed to disclose excess MVP representation among cases of otherwise unexplained SCD.[26,41,42] Furthermore, meta-analyses could not link formally MVP and SCD.[29] Thereafter, isolated MVP prognosis with no or mild DMR has generally been considered benign. However, the cohort studies also revealed heterogeneous MVP outcomes, dominated by DMR severity and LV dysfunction,[19,20] raising the issue of small subsets that may be at risk among MVP without significant DMR that may not be detectable among large cohorts or autopsy registries.

This debate was recently reignited by a small case series of "malignant" bileaflet MVP with little DMR, presenting with cardiac arrest resuscitated and completely negative enquiry for other SCD causes, including genetic testing.[37] (*Table 1*, second rows case series)

Furthermore, patients with MVP, flail leaflet, and significant MR (Grades 3 and 4) but without symptoms or LV dysfunction were noted

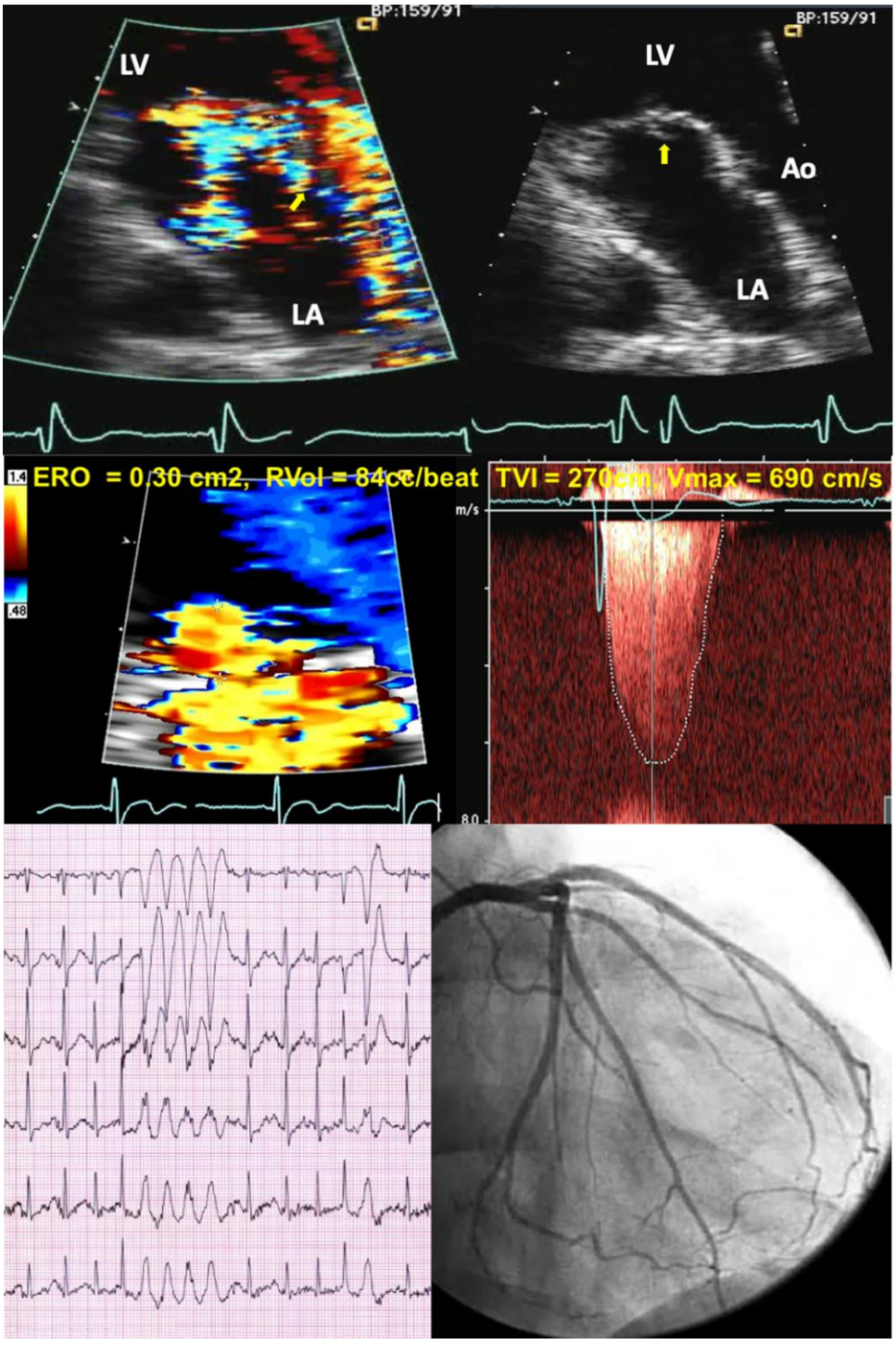


Figure 1 Sudden cardiac death in the context of mitral valve prolapse with moderate-to-severe degenerative mitral regurgitation in a 72-year-old male. (Upper-row) Transthoracic Doppler echocardiography apical three-chamber view in a 72-year-old active and asymptomatic male, displaying a small flail segment of the posterior leaflet (arrow). (Middle-row) Moderate–severe DMR associated, quantified as effective regurgitant orifice 0.30 cm^2, with regurgitant volume 84 mL/beat. (Lower-row left) Burst of ventricular tachycardia at peak exercise testing at 107% of expected. (Lower-row right) Coronary angiogram reported 40% middle left anterior descending and 60% marginal branch obstruction. Ao, aorta; ERO, effective regurgitant orifice; LA, left atrium; LV, left ventricle; RVol, regurgitant volume; TVI, time velocity integral.

to have twice the SCD risk as the general population.[23] However, the question remained whether the SCD occurred *with or because* of MVP and whether an MVP subset could be defined to be at high risk for arrhythmia but small enough to be compatible with the overall benign outcome of MVP with no or mild DMR. This difficult question of causality, in the absence of definite clinical trial, was thus

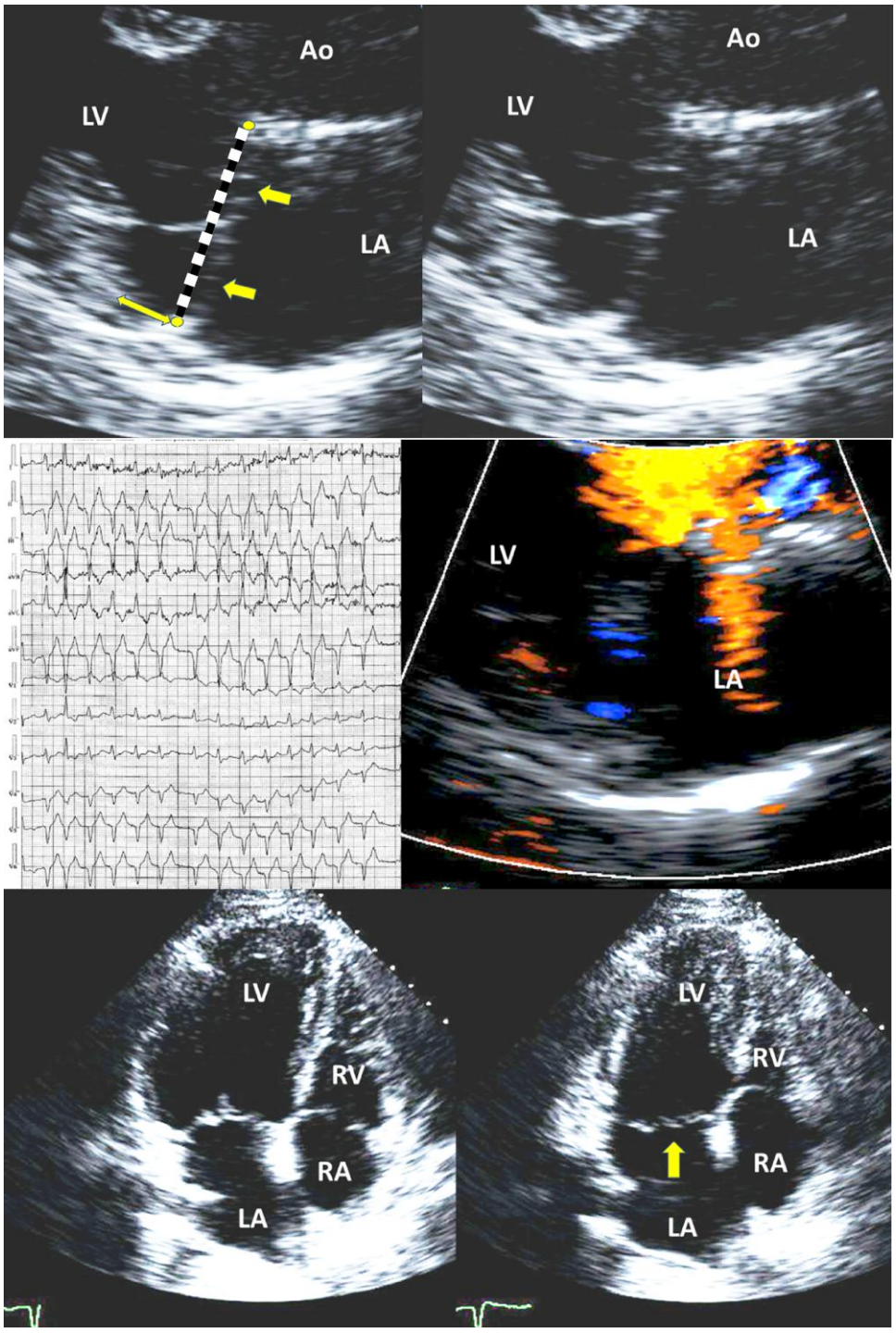


Figure 2 Sudden cardiac death in the context of mitral valve prolapse with trivial degenerative mitral regurgitation in a 26-year-old female. (Upper row) Transthoracic echocardiographic parasternal long-axis view bileaflet mitral valve prolapse in a 26-year-old active female with pre-syncopal episodes displaying notable mitral annular disjunction with (middle row right) trivial DMR. (Lower row) Transthoracic echocardiographic apical four-chamber view showing bileaflet mitral valve prolapse with normal left and right ventricular function. (Middle row left) Holter electrocardiogram monitoring showing numerous episodes of ventricular tachycardia. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

approached based on association of MVP phenotype with ventricular arrhythmias.

In that regard, a phenotype of bileaflet prolapse as marker of "malignant" MVP[29] was found to be associated weakly with arrhythmias and not at all with mortality.[35] Conversely, coherent data from multiple data sources suggested specific MVP features, as markers of an arrhythmic mitral valve prolapse (AMVP) phenotype that may ultimately contribute to SCD. A retrospective cross-sectional study of patients who

Table 1 Relevant studies of mitral valve prolapse–sudden cardiac death link

Study	Year	Design	Association MVP with excess			Phenotype associated	Genetic/ Patho	N MVP
			SCD	Death	VA			
Outcome studies								
Freed *et al.*[3]	1999	Prospective cohort (Framingham)	No	No	No	No	No	84
Grigioni *et al.*[23]	1999	Registry of severe DMR with Flail	Yes	Yes	NA	Symptoms EF	No	348
Avierinos *et al.*[19]	2002	Community cohort (Olmsted County)	No	Yes	NA	MR EF	No	833
Nordhues *et al.*[35]	2016	Referral bi-MVP cohort	No	No (lower)	Yes	Bi-MVP	No	5 669
Antoine *et al.*[20]	2018	Referral MVP cohort	No	Yes	NA	MR	No	3914
Essayagh *et al.*[36]	2020	MVP cohort with Holter monitoring	NA	with VT	Yes	MMVP, MAD, ECG	No	595
Cross-sectional case series								
Sriram *et al.*[37]	2013	Single center SCA	NA	NA	NA	Bi-MVP, female	Genetic testing	10 MVP among 24 SCA
Perazzolo Marra *et al.*[38]	2016	Single center MRI	NA	NA	Yes	MAD, LV Fibrosis		52
Hourdain *et al.*[39]	2018	International SCA registry—9 centers	NA	NA	Yes	Syncope, MMVP, MAD, ECG	No	42
Essayagh *et al.*[40]	2019	Single center MRI	NA	NA	Yes	MAD, Larger MA LV fibrosis	No	89
Smith and Iqbal[32]	2020	Single center SCA	NA	NA	NA	Female, ECG, bi-MVP, not fibrosis	No	6
MVP-focused autopsy studies								
Basso *et al.*[26]	2015	Registry of SCD	Yes: 6.6% SCD with MVP	NA	NA	LV fibrosis	Patho	43 MVP of 650 SCD
Han *et al.*[41]	2020	Matched SCD registry from Australia	No: 0.5% SCD with MVP	NA	NA	Larger MA, cardiac mass: severe MR?	Patho	71
Delling *et al.*[42]	2021	Registry of SCD autopsied	Possible: 2.2% SCD 3.8% SAD with MVP	NA	NA	None		13 MVP among 339 SCD
Meta-analyses								
Nalliah *et al.*[29]	2019	Meta-analysis of SCD in MVP	Uncertain	NA	NA	Bi-MVP, Fibrosis, ECG	No	34 reports
Oliveri *et al.*[43]	2021	Meta-analysis of AMVP features	NA	NA	Yes	Bi-MVP, ECG, MAD		6 reports

AMVP, arrhythmic mitral valve prolapse; bi-MVP, bileaflet MVP; DMR, degenerative mitral regurgitation; EF, ejection fraction; ECG, repolarization abnormalities on electrocardiogram tracings; LV, left ventricle; MA, mitral annulus; MAD, mitral annular disjunction; MMVP, severely myxomatous MVP; MR, mitral regurgitation; MRI, magnetic resonance imaging; MVP, mitral valve prolapse; NA, not assessable; Patho, pathological assessment; SCA, sudden cardiac arrest; SCD: sudden cardiac death; VA, ventricular arrhythmia; VT, ventricular tachycardia.

had recovered from cardiac arrest with no other potential cause than MVP underscored a common phenotype characterized clinically by frequent syncope/pre-syncope, morphologically by severe myxomatous disease with marked redundancy and MAD, and electrocardiographically by frequent ST-T changes and arrhythmias originating from the mitral complex.[39] Furthermore, in a cohort of patients with MVP in whom arrhythmias were quantified by Holter, monitoring suggested a similar association between severity of ventricular arrhythmias and severe mitral myxomatous disease (often but not exclusively bileaflet MVP) with marked leaflet redundancy and frequent MAD detected by echocardiography, as well as frequent ST-T abnormalities.[36] Finally, among these coherent data, MAD detected by magnetic resonance imaging (MRI) was associated with ventricular arrhythmias.[40] Furthermore, myocardial fibrosis detected by MRI is strongly associated with the arrhythmic phenotype.[26,40] These coherent data, confirmed in a meta-analysis,[43] suggested a definite AMVP phenotype that would affect a small subset of patients with MVP at concentrated high risk.

The arrhythmic mitral valve prolapse phenotypes

Arrhythmic mitral valve prolapse is defined per guidelines by the combination of MVP (with or without MAD), with frequent and/or complex ventricular arrhythmia, in the absence of any other well-defined arrhythmic substrate (e.g. primary cardiomyopathy, channelopathy, active ischemia, or ventricular scar due to another defined etiology) regardless of MR severity.[44] This overt AMVP "at risk" for SCD may be preceded by phenotypes not yet associated with overt arrhythmias but "at risk" for developing malignant arrhythmias.

Accordingly, two phenotypes can be identified as follows:

- AMVP due to severe DMR

Patients with MVP and severe MR showed high risk of excess mortality[20] including excess SCD compared with the general population,[23,45] irrespective of valvular morphology. Atrial arrhythmias, reduced LV systolic function, and severe heart failure symptoms are associated with increased SCD risk, but even without such risk factors, MVP with at least moderate-to-severe MR yields excess mortality[46] and SCD, with double the incidence compared to the general population.[23] Surgical MR correction in observational cohorts tends to markedly reduce ventricular arrhythmic events,[47] and SCD rates,[23] and restores life expectancy by reducing overall mortality.[46]

- Arrhythmic MVP with severe myxomatous disease irrespective of DMR

The overall survival of the MVP subset without severe MR or LV dysfunction is overall equivalent to that of the general population.[19] However, patients with severe myxomatous disease with marked redundancy, excess leaflet length/thickness, and MAD, irrespective of DMR severity, are prone to develop arrhythmias over time.[48,49] This phenotype requires careful interpretation of imaging and can also be demonstrated by MRI,[40] which additionally measures myocardial fibrosis severity/location. A small percentage (9%) present with high-risk arrhythmias (VT > 180 b.p.m.), while presentation with frequent extra-systole or slower non-sustained VT (NSVT) is more frequent and sustained VT is quite rare. Patients with pre-syncope or syncope are at particular risk of life-threatening ongoing arrhythmias and should undergo prompt monitoring of long duration. These patients often also present with inferior ST-T changes and premature ventricular complexes (PVCs) generally originating from the mitral complex. This small subset may need consideration for therapy, involving variably mitral repair (with significant DMR) and/or ICD. While patients without overt arrhythmia and this phenotype are at risk of developing arrhythmias in the future, this outcome may take years to develop and, in and by itself, this phenotype is not an indication for therapy but rather for repeated/extended cardiac monitoring. Hence, even in this at-risk AMVP subset, the clinical context is quite heterogeneous and warrants careful identification of MVP arrhythmic complications.

Arrhythmic mitral valve prolapse evaluation: clinical, echocardiographic, and magnetic resonance imaging characterization

- Syncope is uncommon (2%–3.6%) in unselected subjects with MVP[3,50] but reported in 35% of MVP patients with malignant arrhythmias or SCD.[51] Furthermore, in a large MVP cohort, syncope was more frequently reported with documented severe ventricular arrhythmias.[36] Therefore, syncope and particularly unexplained syncope markedly raise the concern for malignant arrhythmias. Palpitations and chest pain are frequent but in similar proportions in MVP with and without ventricular arrhythmias.[36,44]
- Electrocardiographic repolarization abnormalities, such as T-wave inversion (TWI) at rest, often in inferior and lateral leads, are independently associated with AMVP and ventricular arrhythmias.[36] These repolarization abnormalities are thought to be linked to abnormal stretch of papillary muscles and adjacent myocardium and/or locally disturbed repolarization.[44,52]
- Echocardiographic morphologic features of AMVP are severe myxomatous degeneration, defined by thick and redundant leaflets with multi-segment bileaflet MVP and MAD[26,36,38,39] (Figure 3). Importantly, bileaflet MVP, quite prevalent among patients with MVP, is not independently a SCD trigger in large cohorts or population-based studies.[19] Conversely, MAD with MVP is independently linked with ventricular arrhythmias at diagnosis or developing during follow-up.[47] Whether MAD length predicts more frequent arrhythmias is unclear as are MAD-associated arrhythmia mechanisms, although myocardial fibrosis is often noted with longer MAD and hypothesized as causative.
- Cardiac MRI is useful for arrhythmic risk stratification of MVP, due to its unique ability to identify focal myocardial fibrosis using late gadolinium enhancement (LGE). Overall, fibrosis is common in MVP (28%–37%),[53,54] usually located adjacent to the mitral annulus in the basal LV wall including papillary muscles, infero-lateral, and inferior walls[55] (Figure 4). Despite the lack of large cohort assessing LGE in AMVP, multiple studies suggested an association between LGE at the mid-wall of papillary muscles or patchy mid-wall non-ischemic fibrosis in the LV infero-basal region and complex ventricular arrhythmias.[53,54,56,57] Non-invasive assessment of diffuse interstitial myocardial fibrosis with the quantification of extracellular volume (ECV)[58] or a surrogate using post-contrast T1 times[57] has suggested an association with increased risk of complex ventricular arrhythmias. While fibrosis location within the mitral apparatus (papillary muscles and peri-annular region) is considered pathophysiologically associated with arrhythmia in MVP, the diffuse interstitial fibrosis particularly involving the basal segments appears to be a precursor before established replacement fibrosis seen by LGE. Additionally, MRI can identify MAD,[40] yet even by this method, the link between MAD

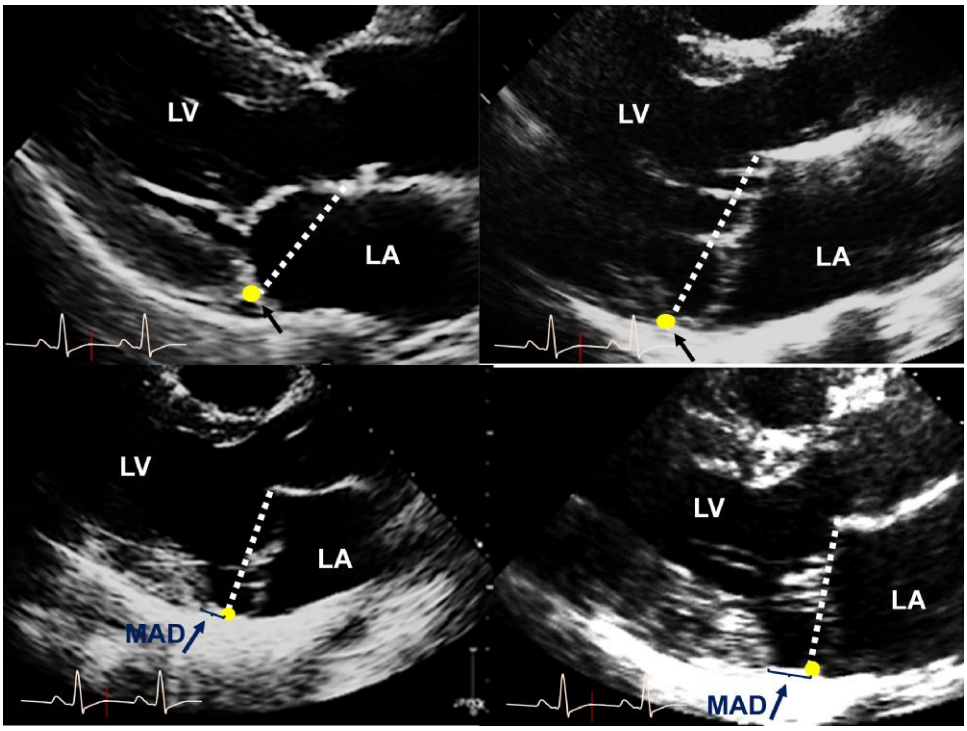


Figure 3 Mitral valve prolapse and mitral annular disjunction by transthoracic echocardiography. (Upper-row left) Transthoracic echocardiographic long-axis view in end-systole displaying normal mitral valve without mitral valve prolapse (upper-row right) with myxomatous bileaflet mitral valve prolapse but no mitral annular disjunction, and myxomatous mitral valve prolapse with mitral annular disjunction of 4 mm length (lower-row left) and of 12 mm length (lower-row right). The dashed line characterizes the mitral annular plane, the yellow dot with single black arrow the insertion of the posterior mitral leaflet mitral annulus, and the single double sided arrow mitral annular disjunction. LA, left atrium; LV, left ventricle; MAD, mitral annular disjunction.

extent and ventricular arrhythmias remains ill defined.[40,59] However, the coherence of echocardiographic and MRI findings points definitely toward the importance of MAD in the development of these arrhythmic complications.

- Computed tomography (CT) scan can be useful to detect MAD, and its extent to P1 and P3 scallops of the posterior leaflet,[55] by taking advantage of its high spatial resolution although it is hindered by lower temporal resolution compared with echocardiography.[60,61] The sub-millimeter isotropic three-dimensional data sets obtained with CT can be useful in assessing the anatomy of fibrous areas of the mitral apparatus and mitral calcifications, important for mitral valve repair.[62]
- Positron emission tomography (PET) MRI imaging of the AMVP demonstrates subclinical myocardial inflammation coexisting with areas of myocardial fibrosis in patients with severe degenerative MR, even in asymptomatic patients. This seminal research warrants further investigation to establish its independent role in the arrhythmic trigger and overall incremental prognostic value in AMVP outcome.[63]

Mitral annular disjunction: pathophysiology and prognostic implication

mitral annular disjunction is a functional alteration of mitral anatomy for which definitions and prevalence reflect considerable uncertainties[15,16,64] (see Supplementary data online, *Table S2*). The normal mitral annulus anatomy involves different attachments for anterior and posterior leaflets. The annulus supporting the anterior leaflet is part of heart's fibrous core in continuity with the fibrous trigones and the aortic annulus. It is highly fibrous and not prone to disjunction from its attachments. Conversely, the annulus portion supporting the posterior leaflet while occupying two-thirds of the circumference is much thinner and is implanted in the ventricular myocardium while supporting the base of the posterior mitral leaflet and the fibrous end of the left atrial wall. Thus, the mitral annulus ensures electric isolation of atrium/ventricle, provides mechanical support for posterior leaflet, and allows appropriate coupling of atrium to ventricular systole.[65]

Confusion arises from definitions of annular disjunction, alternatively reported as microscopic, of limited extent and present in almost all individuals[16] larger but also present in most normal individuals,[66] to macroscopic and part of the slippage associated with myxomatous degeneration of valvular/annular tissue[47,67] (see Supplementary data online, *Table S2*). It is the latter definition which is retained clinically.

Mitral annular disjunction, in the clinical setting, is characterized by macroscopic detachment of the mitral annulus supporting the posterior mitral leaflet from adjacent ventricular myocardium.[68] Hence, MAD is associated with partial loss of mechanical annular function linked dependent on its normal ventricular myocardial attachment while electrical isolation of left atrium/ventricle is maintained.[38,47] Mitral annular disjunction is predominantly observed at insertion of the posterior leaflet, extending laterally variably under all scallops but preferentially under the P2 scallop. Mitral annular disjunction is not uniformly observed in MVP, detectable by echocardiography in approximately one-third of patients.[47] While MAD has been hypothesized as causing

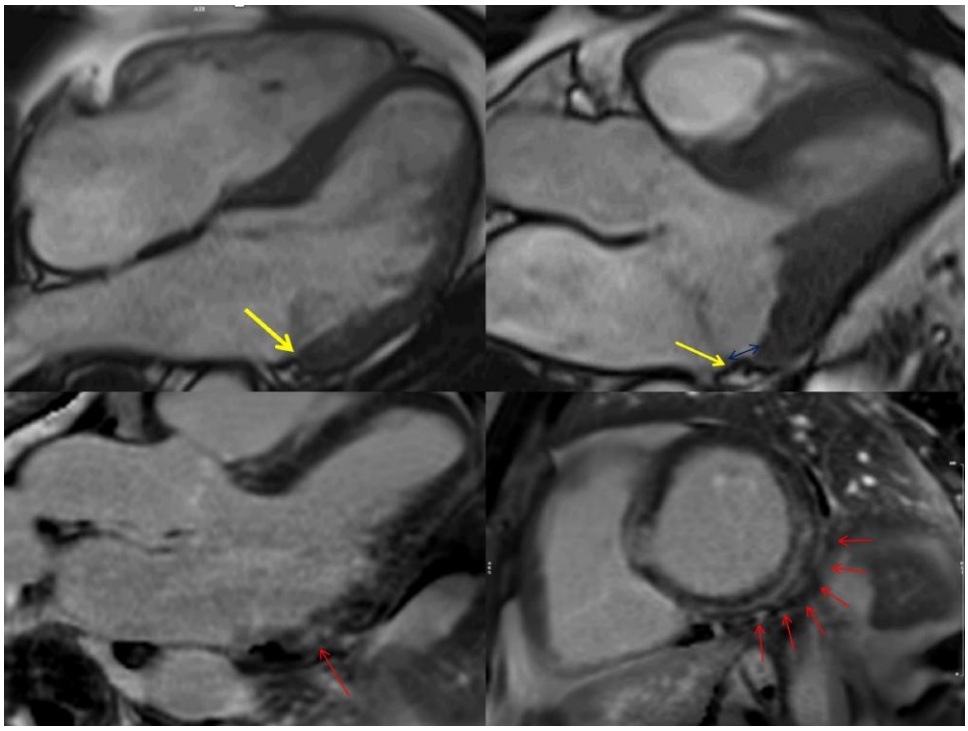


Figure 4 Mitral valve prolapse and mitral annular disjunction by cardiac mitral annular disjunction. (Upper-row left) Cardiac mitral annular disjunction four-chamber view of a 66-year-old male with near-syncope and sustained ventricular tachycardia, normal coronaries, mitral valve prolapse, and moderate mitral regurgitation. Note the thin arrow displaying the insertion of the posterior leaflet on the mitral annulus in mid-diastole. (Upper-row right) Long-axis view in end-systole displaying with bileaflet mitral valve prolapse with mitral annular disjunction and (lower-row left) basal inferior-lateral fibrosis by late gadolinium enhancement. Note the mitral annular plane characterized by the red line, the posterior mitral annulus by the thin single arrow, mitral annular disjunction length by the double sided arrow, and fibrosis by the single thick arrow. (Lower-row right) Short-axis view after late gadolinium enhancement show fibrosis located in the papillary muscles (single thick arrows).

MVP, its inconsistent presence argues in favor of MAD and MVP being variable consequences of myxomatous degeneration.[69] Diagnosis requires high spatial/temporal resolution imaging, in long-axis views by transthoracic echocardiography[59,70–72] or MRI[40,67,72] through dynamic frame-by-frame analysis with careful examination of mitral annulus position[20,44] (*Figure 5*). Mitral annular disjunction depth measurement begins at posterior leaflet insertion on the annulus/left atrial wall and ends at the detached LV myocardium in systole.[40,73] Mitral annular disjunction may occur in any form of MVP but most commonly in advanced myxomatous degeneration with bileaflet MVP, with longer, thicker, and redundant leaflets and larger mitral annulus, independently of all other characteristics.[40,47] The term "curling" is used to refer to the deformation of posterior leaflet assumed to remain attached to the ventricular myocardium, but we find it a misnomer as the annulus is almost completely detached from the myocardium with MAD.[69] Emerging data suggest that tricuspid annular disjunction may coexist with MAD.[74]

Physiologic consequences of MAD include LV remodeling, with larger size, in excess of that justified by DMR, irrespective of age.[40,47,73] This association is understood as consequential to de-anchoring of LV myocardium from the roots of mitral annulus,[75] raising concerns for MAD permanent LV consequences. Potential explanation for excess LV remodeling with MAD includes LV atrophy vs. fibrosis as consequence of annular detachment.[69] Mitral annular disjunction is also associated with abnormal annular movement, widening in late systole (unanchored annulus) tending to enhance the separation of posterior and anterior leaflets.[73,76] While longitudinal data are lacking, MAD likely progresses with aging.[67,77] Progressive detachment may be linked to peri-annular inflammation and possibly to LV basal fibrosis[78] and to arrhythmia development.[79,80] Mitral annular disjunction's clinical link to progressive development of ventricular arrhythmias is now well established.[47] Indeed, patients with MAD at MVP diagnosis have a two-fold increase in the cumulative probability of arrhythmic events and particularly VT compared with those without MAD. Arrhythmic event incidence tends to be progressive, affecting close to one-third of patients 5 years after diagnosis and two-thirds at 10 years after diagnosis but is much higher than in patients without MAD. Thus, MAD at MVP diagnosis is a harbinger of ventricular arrhythmias, but often these are delayed during follow-up, emphasizing the very reassuring absence of excess mortality after MAD diagnosis[36] (*Figure 6*). Thus, with MAD, prudent MVP management should remain the rule. However, once severe ventricular arrhythmias are detected, particularly VT ≥ 180 b.p.m., subsequent excess mortality is observed, warranting appropriate and prompt therapeutic interventions based on the arrhythmias diagnosed (*Figure 6*).[36]

Arrhythmic mitral valve prolapse risk stratification

Risk stratification of AMVP relies first on clinical presentation and cardiac imaging characteristics and therefore dictates the intensity of

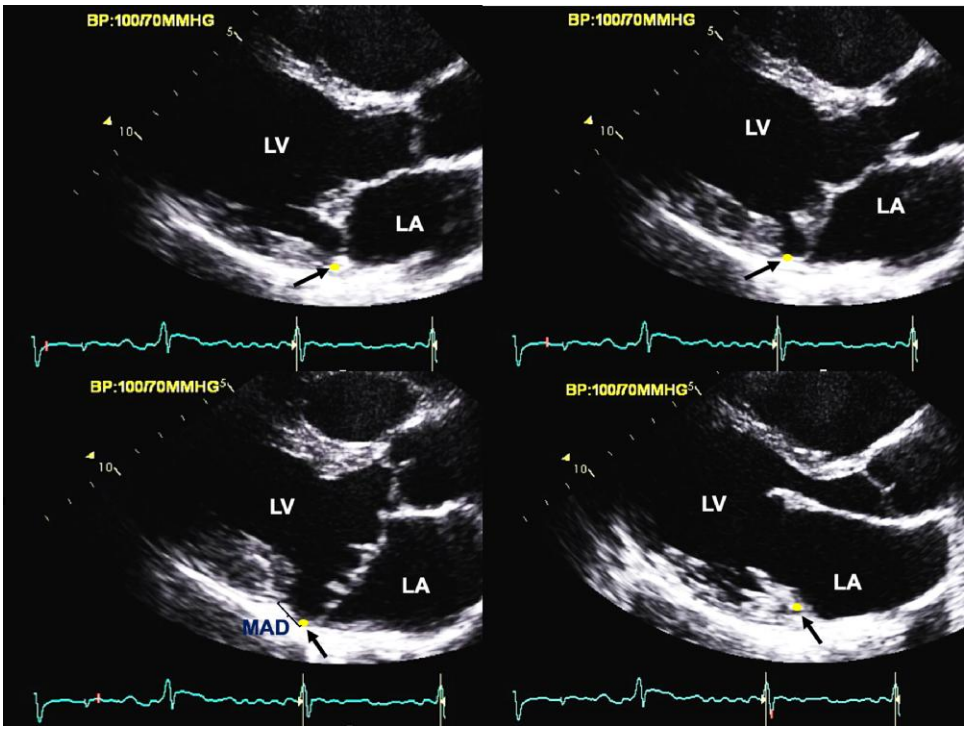


Figure 5 Frame-by-frame analysis of the mitral apparatus by transthoracic echocardiography in parasternal long-axis view within the entire cardiac cycle. (Upper-row left) Yellow dot with single black arrow characterizing the position of the posterior mitral annulus in early systole and (upper-row right) mid-systole. Note the prolapse of the mitral leaflets appearing in mid-systole, more pronounced on the posterior leaflet, and the absence of posterior annular disjunction yet. (Lower-row right) Late-systole view showing bileaflet mitral valve prolapse with mitral annular disjunction (black bracket) defined as a detachment of the posterior mitral annulus (yellow dot single black arrow) from the adjacent left ventricular myocardium. (Lower-row right) Early diastole view showing restored continuity between the insertion of the posterior leaflet on the mitral annulus and the left ventricular myocardium, emphasizing the necessity of image-by-image analysis of the mitral valve for mitral annular disjunction measurement in end systolic view after identification of the insertion of the posterior mitral valve leaflet in early systole. LA, left atrium; LV, left ventricle; MAD, mitral annular disjunction.

arrhythmia screening. The arrhythmia severity detected by monitoring[36,81] then guides both frequency of follow-up and therapeutic interventions (*Graphical Abstract*). Indeed, not all patients with MAD present with arrhythmias,[47] and not all arrhythmias detected are associated with excess mortality.[36] Thus, MVP itself should trigger reassurance in absence of significant DMR, clinical complications, or severe arrhythmia, and detection of MVP phenotype predisposing to arrhythmias or of ventricular arrhythmias of mild or moderate grade represents elevated risk and therefore warrants more frequent rhythm monitoring. Indeed, the arrhythmia detected is the crucial element that will trigger the therapeutic decision and not the MVP phenotype alone. Prompt therapeutic intervention is solely indicated by severe ventricular arrhythmias (and not MAD presence), particularly if those are associated with syncope or pre-syncope.[39]

- Clinical/echocardiographic presentation with pre-syncope or unexplained syncope strongly raises suspicion of ongoing severe arrhythmia. Phenotypic risk features such as negative T waves, severe myxomatous degeneration with redundant leaflets, MAD, or LGE by MRI represent a higher risk of ongoing or future ventricular arrhythmias. Therefore, the clinical and imaging context strongly influences the intensity of rhythm monitoring.[44] For example, patients presenting with unexplained syncope, even without VT on Holter monitoring are prime candidates to undergo extended electrocardiogram (ECG) monitoring by long-duration Holter or preferably implantable loop recorder (ILR), to uncover with highest sensitivity ventricular arrhythmias. It should be noted that the risk–benefit ratio of this intensified rhythmic enquiry remains to be determined.

Conversely, asymptomatic patients without complex ventricular arrhythmia on the initial screening Holter would only require episodic Holter assessment by primary care practitioners, more frequently if they present with phenotypic risk features. Because ventricular arrhythmias may develop secondarily, rhythmic reassessment over time is warranted, and its frequency/intensity depends on presence/number of phenotypic risk features.[44] The role of electrophysiology (EP) studies is unknown but is not considered to replace Holter or ILR monitoring in screening for spontaneous ventricular arrhythmias.[82] Indeed, while induced monomorphic VT is more specific than polymorphic VT, arrhythmia induction by EP studies can be non-specific.[44]

- Arrhythmia severity by Holter is the main determinant of intensity/frequency of repeated rhythmic screening and of medical/surgical therapy. Sustained VT, spontaneous polymorphic NSVT, and rapid NSVT monomorphic (>180 b.p.m.) are considered harbingers of SCD. Polymorphic, frequent, and complex ventricular extra-systole

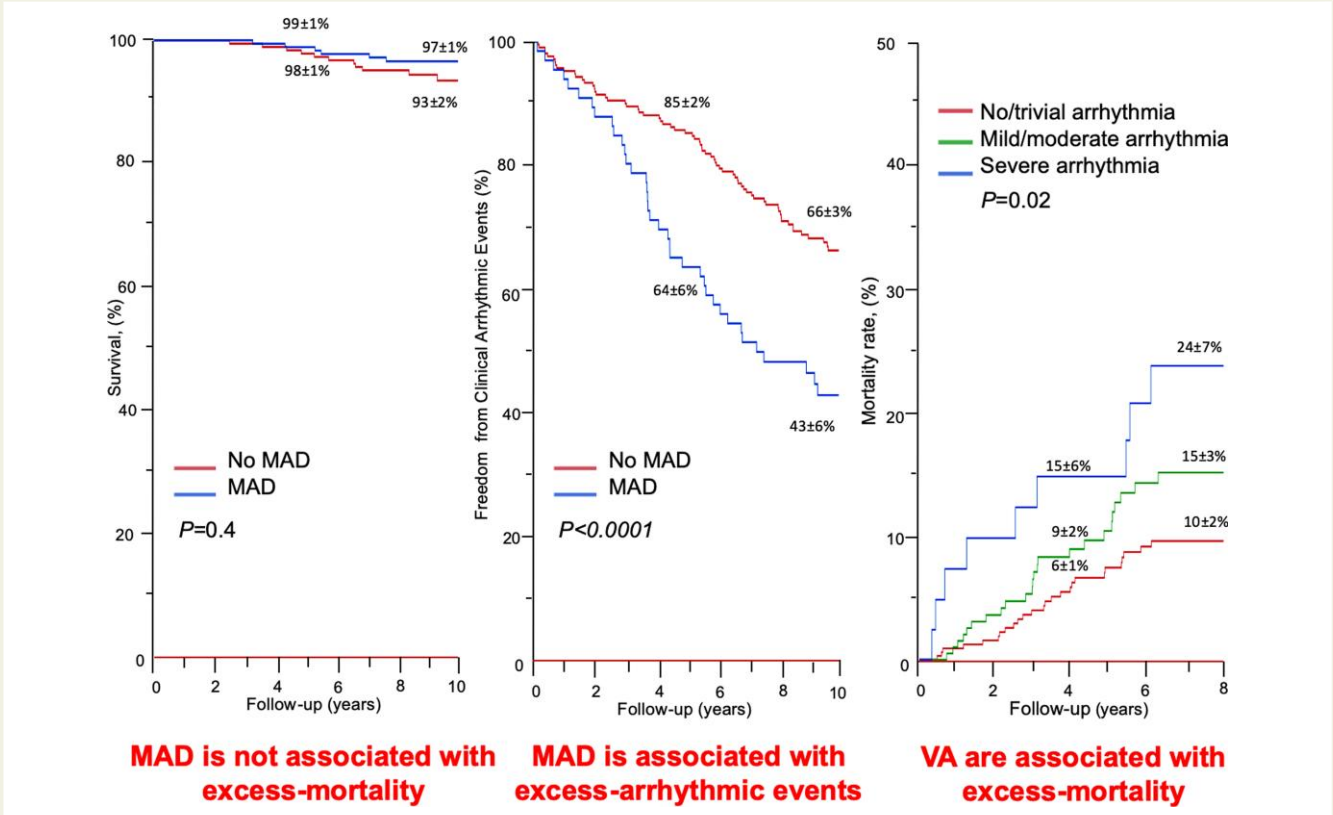


Figure 6 Survival impact of mitral annular disjunction and ventricular arrhythmia long term by mitral annular disjunction presence in age-matched cohort. (Left-panel) Survival stratified by mitral annular disjunction groups of matched age, body mass index, coronary artery disease history, atrial fibrillation, and co-morbidity index. Note the comparable mortality between mitral annular disjunction groups. (Middle-panel) Overall survival free of clinical arrhythmic event stratified by mitral annular disjunction. Note the substantial reduction of arrhythmic event-free survival with mitral annular disjunction presence. (Right-panel) Mortality rate of mitral valve prolapse stratified by ventricular arrhythmia severity in the overall cohort. Note the mortality difference with ventricular arrhythmia severity, considerable when severe. Number indicates estimated survival ± SE. MAD, mitral annular disjunction; VA, ventricular arrhythmia. Modified from Essayagh *et al.*[36,47]

and NSVT monomorphic of lower rate (<180 b.p.m.) are considered intermediate-risk arrhythmias. Isolated frequent monomorphic ventricular extra-systole is considered low risk. In case of asymptomatic MVP without arrhythmia at index Holter, the absence of further phenotypic risk factors will indicate episodic Holter ECG monitoring whereas more frequent monitoring by Holter or ILR is advised in case of multiple phenotypic risk factors. Conversely, the presence of palpitations and/or pre-syncope/syncope without severe VT at index Holter will trigger prompt ILR implantation to guide the therapeutic approach.[44]

Arrhythmic mitral valve prolapse and mitral annular disjunction management

The first consensus on management of AMVP, despite all gaps of knowledge, was recently presented[44] and provides clarification regarding tools and aims of management. Long-term follow-up/medical therapy is advocated for the frequent low-risk ventricular arrhythmias in MVP,[36] but while high burden of ventricular ectopy is considered associated with increased mortality in the general population,[83] there is no evidence that prophylactic treatment aimed at suppressing extra-systole in asymptomatic MVP is beneficial.[44] However, medical therapy aiming at suppressing extra-systole is advised in suspected PVC-induced cardiomyopathy, with low LV ejection fraction unrelated to DMR and in symptomatic patients regardless of LV function.[84] Beta-blockers and verapamil improve symptoms but result in modest reduction of PVC burden. Flecainide, propafenone, and amiodarone yield more potent PVC burden reduction with frequent improvement in LV function.[85–87] The potential benefit from amiodarone must be balanced against adverse effects associated with long-term treatment. Sotalol reduces PVC burden but may not improve LV function.[44]

The role of ICDs for primary prevention of SCD in patients with MVP/MAD is unresolved. It is a relative consensus that primary ICD implantation is to be promptly considered in patients with the AMVP phenotype and high-risk VT. The benefit of primary ICD implantation in patients who underwent mitral repair for severe DMR complicated by high-risk VT preoperatively is also to be considered, but, in both contexts, clinical trials and cohort studies will be essential in defining the benefit from ICD implantation. Similarly, primary ICD implantation in patients with AMVP phenotype and persistent VT despite transcatheter ablation is generally considered appropriate but still warrants rigorous evaluation. Conversely, ICD implantation for secondary prevention is considered appropriate in patients with MVP and resuscitated sudden cardiac arrest.

Transcatheter ablation of VT has been performed in patients with AMVP and generally involved papillary muscles or Purkinje system

foci and can be succesful.[88–91] On the other hand, long-term success rates for ventricular extra-systole ablation in MVP range between 60% and 84%,[88,89,92–94] and its role in preventing sudden arrhythmic death is uncertain. Premature ventricular complex ablation has been performed in patients with refractory symptoms due to frequent extra-systole,[95,96] or with extra-systole-induced LV dysfunction,[93] but the potential of these therapies to improve outcome is uncertain. For AMVP with frequent extra-systole, severe DMR, and reduced LV function, the guideline-based indication of surgical mitral valve repair should not be delayed by considerations of arrhythmia ablation.

Mitral valve repair in patients with significant DMR is often the first therapeutic consideration and is associated with decrease in arrhythmia frequency and incidence of sudden death.[23,36] Post-operatively, presence of residual arrhythmias should be evaluated and ICD indication re-appraised. This trend for arrhythmia rate reduction post-mitral surgery may be important to consider in future clinical trials[36] and may be linked to MAD disappearance in almost all operated patients,[47,73] achieved with suture of ring/prosthesis joining annulus to LV myocardium and collapsing the MAD gap. While transcatheter edge-to-edge repair (TEER) has been recently shown to improve survival of high-risk patients with MVP and severe DMR,[97] its potential in yielding reduced ventricular arrhythmia incidence remains to be demonstrated. Furthermore, TEER cannot address the annular–myocardial separation of MAD, while surgical mitral repair allows, most often, correction of MAD by suturing the ring annuloplasty.[73] Thus, in the context of MVP with MAD, with moderate-or-severe DMR, and with or without high-risk VT, surgical mitral repair is the preferred therapeutic approach. Guideline-based management remains effective in DMR patients without serious arrhythmias.

Future developments: long-term follow-up, cohorts, and trials

With improving knowledge of AMVP, new questions appear and new research targets are being proposed.[98] Because Holter monitoring has not been recommended for evaluation of MVP and DMR in clinical guidelines, the volume of data regarding AMVP remains modest[36] and new cohorts involving systematic/prolonged rhythmic monitoring are warranted to address the entire spectrum of MVP. Furthermore, increased sensitivity and safety level of prolonged monitoring by ILR vs. Holter remain undefined and warrant clinical trials. While important facts regarding AMVP have been brought to light by existing observational cohorts, the incidence and thresholds for severe arrhythmias have to be objectively defined by large prospective MVP cohorts with systematic arrhythmia monitoring and long-term follow-up. These would allow a systematic combination of comprehensive imaging using both echocardiography and MRI to truly define the independent markers of the AMVP phenotype. Now that a comprehensive genetic basis for MVP has been described,[99] such comprehensive cohort may include genetic and biomarkers analysis and allow investigating using artificial intelligence whether specific genes are linked to the AMVP phenotype[100,101] for the development of ventricular arrhythmias, particularly those associated with myopathic characteristics. The pathophysiology of AMVP suggestive of repetitive traction (mechanical hypothesis) or degeneration due to slippage/traction causing fibrosis leading to arrhythmia will ultimately be resolved by such cohorts. Progression of MAD and ventricular arrhythmias over time and their potential link to DMR severity progression have not been yet investigated and warrant repetitive AMVP echocardiographic examination and rhythmic monitoring. Regarding ventricular arrhythmia occurrence, seminal studies showed that exercise-induced ventricular arrhythmias are in general associated with an increased risk of all-cause and cardiovascular mortality.[102–104] However, such link exercise-induced arrhythmia to SCD remains unknown in the specific context of MVP patients, and whether exercise-induced arrhythmias may help stratification of the arrhythmic risk in these patients will require future cohorts with long-term follow-up. In patients with high-risk VT associated with MAD and moderate DMR,[47] the role of surgical repair while attractive is not formally defined. More generally, DMR correction in patients with MAD and substantial DMR (≥moderate?),[20] in the context of AMVP, using surgical repair rather than TEER, which does not involve annular suture, has not been the subject of a clinical trial to measure its benefit in term of arrhythmias.

Overall, we have reached the stage of identifying a clinical problem previously poorly defined and an unmet need for therapy. Future clinical trials need to be conducted to define the benefits of medical, rhythmic, and surgical therapies in AMVP,[105] to define beneficial therapies and avoid "excessive" interventions and ultimately create documented guidelines for diagnosis, management, and treatment of AMVP.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

J.L.C. has received consulting fees from 4C Medical, Abbott Structural, Anteris, AriaCV, Boston Scientific, Edwards Lifesciences, Medtronic, VDyne, WL Gore, and Xylocor and has received research grant support from Abbott Northwestern Hospital Foundation, Abbott Structural. M.E.-S. received consulting fees from Edwards, Cryolife, and Mardil. The other author reports no conflicts of interest.

Data Availability

No data were generated or analyzed for or in support of this paper.

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