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EDITORIAL COMMENT

The Arrhythmic Mitral Valve Prolapse

Still a Long Way to Go*

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Mitral-valve-prolapse (MVP) is the most frequent valve condition in Western countries,[1] and remains, as a group, a benign condition in the absence of significant mitral regurgitation (MR) and/or its adverse myocardial consequences affecting its outcome.[2] Sudden cardiac death (SCD) has been observed with significant MR,[3] particularly in patients with heart failure symptoms or ventricular dysfunction, and more rarely in uncomplicated degenerative MR. In patients with MVP and lesser degrees of MR, the risk of SCD has remained a conundrum. On the one hand, because its description is based on auscultatory findings, reports have alternated between descriptions of few complications and case reports of SCDs. Although it is tempting to presume a link between MVP and SCD, establishing scientific causality is more complicated, requiring larger cohorts with comprehensive echocardiographic and rhythmic description.

Adding to the confusion regarding the association of MVP and SCD are the facts that SCD is fortunately a rare clinical event, making it a difficult endpoint to analyze in clinical cohorts, and that, once SCD has occurred, it is challenging to accurately define cause and mechanisms. Also, MVP is a condition with considerable heterogeneity, affecting the severity of myxomatous degeneration, of the prolapse, of the degree of degenerative MR, and of the magnitude of ventricular/atrial responses to the MVP/MR, among other factors.[2] To try to resolve this conundrum, population-based cohorts described a generally benign outcome of MVP with no or mild MR and normal ventricular function.[1,2] The normal life expectancy in this subset of MVP argued against a high incidence of SCD associated with MVP and was confirmed in large clinical practice cohorts,[4] all arguing against an ominous SCD association. However, small case series of SCD with MVP unexplained by any other potential cause, raising the concern of an arrhythmic MVP subset independent of the MR degree, have renewed the interest in investigating the association SCD with MVP.[5] Defining whether SCD may occur "*because*" vs "*with*" MVP in an obligatory small subset of patients (good outcome in the larger no/mild MR subset of MVP) is complex and is a process that remains ongoing. This has involved several lines of investigation, such as examining SCD registries to define a potential excess proportion of MVP,[6] or by analyzing a potential common MVP phenotype associated with SCD[7] and with serious ventricular arrhythmias,[8] or by examining the incidence of serious ventricular arrhythmias development associated with specific MVP features.[9] Although much knowledge has been gained in recent years and more clarity has been achieved in defining the arrhythmic MVP, its diagnosis, and potential therapeutic options[10] it is essential to continue accumulating data to clarify this condition and focus our clinical attention on those truly requiring it.

THE PRESENT REPORT

The paper by Alqarawi et al[11] in this issue of *JACC: Clinical Electrophysiology* aimed to report the prevalence and characteristics of MVP patients in a multicenter registry of initially unexplained cardiac arrest

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patients and compare the characteristics of those with and without an alternative explanation for cardiac arrest. In a registry of 571 patients with unexplained cardiac arrest, the prevalence of MVP in patients with idiopathic ventricular fibrillation (IVF) was 6.6%. Two phenotypes of MVP are described, one associated with IVF (ie, arrhythmic mitral valve prolapse [AMVP], n = 24) and the other with other identified cause for cardiac arrest (n = 5), considering these MVPs as likely innocent bystanders. The clinical and electrical characteristics of IVF patients with MVP (ie, AMVP) and without MVP were comparable. AMVP patients, compared with nonarrhythmic MVP patients more frequently had bileaflet MVP, and had a tendency to more frequent mitral annular disjunction (MAD), PVCs, and family history of SCD. Among patients with IVF and available follow-up, higher proportion of patients with MVP tended to receive appropriate ICD therapies compared with those without MVP with a higher proportion of cardiac arrest during exercise among AMVP patients.

The study is important in reporting the excess prevalence of MVP among cases of SCD, which has been quite discordant in previous published reports[6] but remains limited by the small number of MVP patients included, profoundly hindering the analysis of the phenotype of MVP associated with SCD.

Irrespectively, this study reinforces the previously noted importance of myxomatous disease with bileaflet MVP in AMVP.[8] It suggests more frequent family history of SCD among AMVP patients and confirms several phenotypic features associated with AMVP.[8] Those involve severe myxomatous disease with marked redundancy, excess leaflet length/thickness, MAD, and fibrosis by magnetic resonance imaging, irrespective of DMR severity. These patients often also present with inferior ST-T changes and premature ventricular complexes generally originating from the mitral complex.

WHAT IS NEXT?

With our knowledge of AMVP improving, new questions appear that will ultimately be answered by future research.[12] Because Holter monitoring has not been recommended for evaluation of MVP and DMR in clinical guidelines, the volume of data regarding AMVP remains modest,[8] and new cohorts involving systematic/prolonged rhythmic monitoring are warranted. Only a small percentage (9%) present with high-risk arrhythmias (ventricular tachycardia [VT] >180 beats/min), but new high-risk features need to be more clearly defined.[10] Presentation with frequent extrasystole or slower nonsustained VT is more frequent and sustained VT is quite rare, but the features that require more frequent or prolonged rhythm monitoring are poorly defined. Conversely, patients with unexplained presyncope or syncope are concerning for imminent life-threatening arrhythmias and should undergo prompt monitoring of long duration. The subsets that may need consideration for therapy, involving variably mitral repair (with significant DMR) and/or implantable cardioverters,[10] are ill-defined. Although patients with the "AMVP 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/prolonged cardiac monitoring.

Although 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, along with a systematic combination of comprehensive imaging using both echocardiography and magnetic resonance imaging, would allow us to truly define the independent markers of the AMVP phenotype. Now that a comprehensive genetic basis for MVP has been described, such a comprehensive cohort may include genetic and biomarkers analysis and allow investigation using artificial intelligence into whether specific genes are linked to the AMVP phenotype for the development of ventricular arrhythmias, particularly those associated with myopathic characteristics. The pathophysiology of AMVP is suggestive of repetitive traction (mechanical hypothesis) or degeneration caused by slippage/ traction causing fibrosis leading to arrhythmia, which 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 yet been investigated and warrant repetitive AMVP echocardiographic examination and rhythmic monitoring. Regarding ventricular arrhythmia occurrence, seminal studies showed that exercise-induced ventricular arrhythmias may be at increased risk of mortality. However, such a link between exercise-induced arrhythmia and SCD remains undefined in the specific MVP context, and whether exercise-induced arrhythmias may help stratification of the arrhythmic

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risk in these patients will require future cohorts with long-term follow-up.

Overall, we have reached the stage of identifying a clinical problem previously poorly defined, for which the therapeutic approach remains poorly defined. Future clinical trials are warranted to define the benefits of medical, rhythmic, and surgical therapies in AMVP and avoid "excessive" interventions to ultimately provide the cardiology community with clear guidelines for diagnosis, management, and treatment of AMVP.

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REFERENCES

1. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med*. 1999;341:1–7.

2. Avierinos JF, Gersh BJ, Melton LJ 3rd, et al. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation*. 2002;106:1355–1361.

3. Grigioni F, Enriquez-Sarano M, Ling L, et al. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol*. 1999;34:2078–2085.

4. Antoine C, Benfari G, Michelena HI, et al. Clinical outcome of degenerative mitral regurgitation: critical importance of echocardiographic quantitative assessment in routine practice. *Circulation*. 2018;138:1317–1326.

5. Sriram CS, Syed FF, Ferguson ME, et al. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2013;62:222–230.

6. Basso C, Perazzolo Marra M, Rizzo S, et al. Arrhythmic mitral valve prolapse and sudden cardiac death. *Circulation*. 2015;132:556–566.

7. Hourdain J, Clavel MA, Deharo JC, et al. Common phenotype in patients with mitral valve prolapse who experienced sudden cardiac death. *Circulation*. 2018;138:1067–1069.

8. Essayagh B, Sabbag A, Antoine C, et al. Presentation and outcome of arrhythmic mitral valve prolapse. *J Am Coll Cardiol*. 2020;76:637–649.

9. Essayagh B, Sabbag A, Antoine C, et al. The mitral annular disjunction of mitral valve prolapse: presentation and outcome. *J Am Coll Cardiol Img*. 2021;14(11):2073–2087.

10. Sabbag A, Essayagh B, Barrera JDR, et al. EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC Council on Valvular Heart Disease and the European Association of Cardiovascular Imaging. *Europace*. 2022;24(12):1981–2003.

11. Alqarawi W, Tadros R, Roberts JD, et al. The prevalence and characteristics of arrhythmic mitral valve prolapse in patients with unexplained cardiac arrest. *J Am Coll Cardiol EP*. 2023;9(12):2494–2503.

12. Essayagh B, Sabbag A, El-Am E, Cavalcante JL, Michelena HI, Enriquez-Sarano M. Arrhythmic mitral valve prolapse and mitral annular disjunction: pathophysiology, risk stratification, and management. *Eur Heart J*. 2023;44:3121–3135.

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