Heart Valve Society
Mitral Tricuspid Valve
Database

Heart Valve Society Mitral Tricuspid Valve Database Project

Project Application

Centers: IRCCS San Raffaele Scientific Institute, Milan, Italy; Leiden University Medical Center, The Netherlands; Medical University of Innsbruck, Austria

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Title of the project application: The evolution of ventricular arrhythmias after mitral valve surgery in patients with Mitral Valve Prolapse and an Implantable Cardioverter Defibrillator: a multicenter retrospective study with long-term continuous rhythm monitoring

Introduction

Mitral valve prolapse (MVP), defined as a systolic abnormal displacement of mitral leaflet free edge above the annular plane at the end of systole [1], is a common finding at echocardiographic examination, with a reported prevalence around 2–3% [2]. As already noticed in Barlow's first studies [3], a subgroup of MVP patients, namely young females with T wave inversion in infero-lateral leads at ECG [4], shows an increased risk of malignant ventricular arrhythmias (VA) and sudden cardiac death (SCD). This association has been subsequently proven by different reports [5, 6], even autoptic [7], who identified bileaflet prolapse in up to 70% of patients with MVP experiencing SCD before 40 years of age.

A recent renewed interest in this topic has fostered the identification of a specific "malignant arrhythmic MVP" phenotype. Patients more prone to develop VA and SCD usually have echocardiographic characteristics of Barlow's disease [thickened, redundant leaflets, bileaflet prolapse, elongated chordae, with or without mitral annular disjunction (MAD)] [2, 8], myocardial fibrosis at papillary muscles and infero-basal left ventricular wall (both at cardiac magnetic resonance imaging [9] and autoptic studies [6, 7]) and left ventricular contraction abnormalities (Pickelhaube sign [10] and left ventricular mechanical dispersion as assessed by speckle-tracking echocardiography [11]). Interestingly, electrophysiological studies mapped the site of VA origin in the same regions where myocardial fibrosis is usually detected [12]. Mitral regurgitation (MR) has surely a role in arrhythmogenesis in this context [13], even if the association between MVP and malignant arrhythmias has been proven even in absence of hemodynamically significant MR [6, 9].

Recently, the European Heart Rhythm Association (EHRA) published a consensus to summarize the latest evidence in this field, providing a common strategy to recognize and treat patients with MVP

experiencing VA [14]. However, the effect of mitral surgery on the recurrence of malignant VA in patients with MVP and VA is unknown. In fact, only case reports and retrospective series have been historically published on the subject, with controversial results.

In a preliminary prospective experience including 88 subjects, almost one third of Barlow's patients undergoing mitral valve (MV) repair showed a significant burden of VA. Among them, 55% experienced VA reduction after surgery [15]. However, the design of the study employed 24-hours Holter ECG monitoring (one before, and three at different time points after surgery) as VA recording tool. Consequently, a continuous rhythm monitoring was not feasible. Moreover, the enrolled population consisted of all-comers Barlow's patients, with different arrhythmic risk profiles [14], while the prevalence of patients with severe, high-risk VA was small: 19 patients (21.6%) had documented NSVT episodes and 4 patients (4.5%) had an implantable cardioverter-defibrillator (ICD) as a secondary prevention tool (3 patients with history of VF and one with history of symptomatic VT). Evaluating the effects of surgery in this specific subgroup is however of outmost importance since these are the subjects with the highest risk of SCD, who may benefit more from the antiarrhythmic effect of surgery, if any.

To the best of our knowledge, a focused analysis in this subgroup is missing, and the largest published case-series of MVP patients with ICD undergoing MV surgery enrolled only 8 subjects. [16]

The use of continuous monitoring devices, such as ICDs, would provide a more accurate and complete picture of the arrhythmic profile of MVP patients, both before and after mitral surgery.

Aim of the project

To evaluate the incidence, type and predictors of recurrent sustained VA in MVP patients with an ICD for secondary prevention of SCD undergoing mitral valve surgery

Included patients

Inclusion criteria:

- *> 18 years old at the time of surgery;*
- *patients with MVP (17) and severe or moderate to severe MR (18), who underwent MV surgery (both repair or replacement);*
- *carriers of an ICD implanted before or immediately after surgery, but only if the major arrhythmic event that triggered ICD implantation (VT/VF/out of hospital cardiac arrest) happened before surgery;*
- *At least one follow-up (clinical, echocardiographic and of the rhythm monitoring device) available after surgery.*

Exclusion criteria:

- *emergent operations;*
- *patients with left ventricular ejection fraction <45 % before surgery;*
- *patients with left ventricular end-diastolic diameter > 70 mm;*
- *patients with left ventricular end-systolic diameter > 50 mm;*
- *patients with history of ischemic heart disease;*
- *patients who underwent concomitant coronary artery bypass grafting, ventricular reconstruction or aortic valve replacement for severe aortic stenosis*

- *patients with any other arrhythmic substrate including arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, long QT syndrome, Brugada Syndrome, dilated cardiomyopathy, left ventricular noncompaction, cardiac sarcoidosis, myocarditis;*
- *patients affected by endocarditis.*

Duration project

x Retrospective □ Prospective

Inclusion period (date of surgery): 1999 -2024

Follow-up period (after surgery): 1999 -2025

We aim at enrolling at least 100 subjects

Primary outcomes

The primary outcome is the absence of a significant arrhythmic burden at follow-up [i.e. no registered episode of SCD, cardiac arrest, sustained ventricular tachycardias (SVT), or ventricular fibrillation (VF) during the observation period] [14].

Secondary outcomes

The study population will be divided in two groups: patients who experience an improvement in VA burden and those in which VA remain stable or worsen. Secondary outcomes include:

- *need for transcatheter ablation;*
- *need for escalation of antiarrhythmic therapy;*
- *post-operative PVB burden ≥ 5%;*
- *occurrence of post-operative non-sustained ventricular tachycardias (NSVT)*

The annual rate of VA after surgery [including NSVT, SVT, VF, anti-tachycardia pacing (ATP) attempts and ICD shocks)], together with clinical, echocardiographic, MRI-assessed (i.e. myocardial fibrosis, if available) and surgical (including mitral repair vs replacement) predictors of VA burden improvement/worsening will also be investigated.

Collection of data outside standard of care

Baseline characteristics should include clinical data, ECG findings, ICD record analysis, transthoracic or transesophageal echocardiographic features (including MAD characterization), cardiac fibrosis investigation (if CMR/cardiac CT scan available) and antiarrhythmic drugs. Registered in-hospital outcomes will be procedural data (i.e. surgical repair technique, concomitant procedures, etc…), post-operative complications and echocardiographic and clinical information (including residual MAD, if any, and antiarrhythmic therapy) at discharge. Follow-up data should include clinical status, echocardiographic data (residual MR, left ventricular ejection fraction), ICD record analysis and antiarrhythmic drugs (if any).

VA will be centrally assessed by a Clinical Events Committee (CEC, responsible person: Marta de Riva Silva, MD, PhD, Leiden University Medical center). For this reason, ICD reports will be collected outside CASTOR EDC. This data encompasses ICD reports in PDF format. The HVS data management team, as joint data controller, will act as data repository for this data, in which responsibilities of joint controllership stipulated in the CSSA apply. Data will be sent to HVS via secured electronic transfer systems. Data storage will be done on secured environment within Erasmus MC, where the VRN are hosted. Centers participating in this project agree to the fact that the proposing researchers may link outcomes of patients to individual centers. Centers must remove all patient identifying information (i.e. patient name, birth data) from the PDF files. The additional files contain the same pseudonymized Patient ID as the database Patient ID.

Classification of VA events will be performed by the CEC. According to the 2022 European Society of Cardiology (ESC) guidelines on the management of VA and prevention of SCD [19], a NSVT will be defined as a run of consecutive ventricular beats lasting 3 beats to 30 seconds. A sustained monomorphic ventricular tachycardia (SMVT) will be defined as a rhythm originating from the

ventricles, with the same beat-to-beat QRS morphology or cycle length (CL) and intracardiac electrogram morphology when recorded on ICD, lasting longer than 30 seconds or requiring intervention for termination. According to their CL, SMVTs will be defined as fast when the CL is < 320ms and slow when the CL ≥ 320ms. Ventricular fibrillation will be defined as a chaotic rhythm without discrete QRS complexes on the surface ECG or, for ICD-recorded episodes, as a ventricular rhythm with beat-to-beat variation in the cycle length and morphology of the intracardiac electrogram. All ICD-treated episodes, whether managed with ATP or shocks, will be reviewed to exclude inappropriate therapies and to evaluate the type of VA.

Echocardiographic imaging should be analyzed by experienced echocardiographers to report the presence and length of MAD (systolic or both systolic and diastolic) [20], leaflet characterization, leaflet thickness, and the presence of systolic curling. [10, 11] If a CMR/cardiac CT scan is available, fibrosis sites should be identified and reported.[9]

Variables entered

All information (except ICD reports, see above) will be entered in the HVS database. A dedicated database will be provided with the list of all the variables required for our purpose.

Statistical analysis

Categorical data will be described as absolute and percentage (%) frequency values and compared with the χ^2 or the Fisher exact tests, as appropriate. The Shapiro–Wilk test will be used to assess whether the distribution of each variable is normal or not-normal. Continuous normally distributed variables will be expressed as mean ± standard deviation (SD) and compared with paired t-test or t-test for independent samples. Continuous not-normal variables will be reported as median (25th percentile; 75th percentile) and compared with Wilcoxon signed-rank test for related samples or with Mann–Whitney test for unrelated samples. Incidence rates along with 95% confidence intervals will be calculated at baseline and at follow-up for each outcome (occurrence of PVB burden ≥ 5%, NSVT, SVT, cardiac arrest, ATP attempts and ICD shocks) per 100 person-years at risk.

Univariable Cox regression will be performed to identify predictors of VA burden reduction. Variables with a P-value <0.15 or <0.20, selected based on clinical relevance, will be included in the multivariable analysis. Subsequently, a multivariable Cox regression model with stepwise selection will be applied to manage confounding factors, isolating the independent effects of the considered predictive variables and reducing the risk of bias.

To assess freedom from VA events, we will use survival analysis, such as the Cox model, to account for patient censoring. We will also consider using competing risk curves (Aalen-Johannesn Estimator) to illustrate the incidence of VA in the presence of competing events. To account for the repeated nature of VA events during the observation periods, we will perform recurrent event analysis using the Poisson regression model. Missing data management will be carefully evaluated after data collection to avoid bias, and specific missing imputation techniques will be performed if required.
A P-value of <0.05 will be used to define statistical significance.

Participating centers

Cardiac surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy

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Medical University of Innsbruck, Austria
Leiden University Medical Center, Leiden, The Netherlands
More centers to come

References

1. Lancellotti EP, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA et al.; On behalf of the Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.
2. Delling FN, Vasan RS. Epidemiology and pathophysiology of mitral valve prolapse: new insights into disease progression, genetics, and molecular basis. Circulation 2014;129:2158–70.
3. Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks. An analysis of 90 patients. Br Heart J 1968;30:203–18.
4. Nalliah CJ, Mahajan R, Elliott AD, Haqqani H, Lau DH, Vohra JK et al. Mitral valve prolapse and sudden cardiac death: a systematic review and meta-analysis. Heart 2019;105:144–51.
5. Sriram CS, Syed FF, Ferguson ME, Johnson JN, Enriquez-Sarano M, Cetta F et al. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. J Am Coll Cardiol 2013;62:222–30.
6. Basso C, Iliceto S, Thiene G, Perazzolo Marra M. Mitral valve prolapse, ventricular arrhythmias, and sudden death. Circulation 2019;140: 952–64.
7. Basso C, Perazzolo Marra M, Rizzo S, De Lazzari M, Giorgi B, Cipriani A et al. Arrhythmic mitral valve prolapse and sudden cardiac death. Circulation 2015;132:556–66.
8. Van Wijngaarden AL, de Riva M, Hiemstra YL, van der Bijl P, Fortuni F, Baxet JJ et al. Parameters associated with ventricular arrhythmias in mitral valve prolapse with significant regurgitation. Heart 2021;107:411–8.
9. Constant Dit Beaufils AL, Huttin O, Jobbe-Duval A, Senage T, Filippetti L, Piriou N et al. Replacement myocardial fibrosis in patients with mitral valve prolapse: relation to mitral regurgitation, ventricular remodeling, and arrhythmia. Circulation 2021;143:1763–74.
10. Muthukumar L, Rahman F, Jan MF, Shaikh A, Kalvin L, Dhala A et al. The Pickelhaube Sign: novel echocardiographic risk marker for malignant mitral valve prolapse syndrome. JACC Cardiovasc Imaging 2017;10: 1078–80.
11. Ermakov S, Gulhar R, Lim L, Bibby D, Fang Q, Nah G et al. Left ventricular mechanical dispersion predicts arrhythmic risk in mitral valve prolapse. Heart 2019;105:1063–9.
12. Vergara P, Altizio S, Falasconi G, Pannone L, Gulletta S, Della Bella P. Electrophysiological substrate in patients with Barlow's disease. Arrhythm Electrophysiol Rev 2021;10:33–7.
13. Grigioni F, Enriquez-Sarano M, Ling LH, Bailey KR, Seward JB, Tajik AJ et al. Sudden death in mitral regurgitation due to flail leaflet. J Am Coll Cardiol 1999;34:2078–85.
14. Sabbag A, 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 endorsed by the Heart

Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society. *Europace.* 2022;24(12):1981-2003.

15. Ascione A, Azzola Guicciardi N, Lorusso R, Boccellino A, Lapenna E, et Al. The impact of mitral valve surgery on ventricular arrhythmias in patients with Barlow's disease: preliminary results of a prospective study. *ICVST* 2023, 36;5.
16. Vaidya VR, DeSimone CV, Damle N, et al. Reduction in malignant ventricular arrhythmia and appropriate shocks following surgical correction of bileaflet mitral valve prolapse. *JICE* 2016;46(2):137-143.
17. Anyanwu AC, et al. Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. *STCS*. 2007;19(2):90-96.
18. De Bonis M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. *EHJ*. 2016;37(2):133-139.
19. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022 Oct 21;43(40):3997-4126. doi: 10.1093/eurheartj/ehac262. PMID: 36017572.
20. Faletra FF, Leo LA, Paiocchi VL, et al. Morphology of Mitral Annular Disjunction in Mitral Valve Prolapse. *JASE*. 2022;35(2):176-186.