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FACTORS PREDICTING THE RISK OF VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH MITRAL VALVE PROLAPSE

Tudoran Cristina[1-3], Florica Voiță-Mekeres[4,5*], Ioan Bogdan Voiță[6], Paula Marian[7], Alin Ovidiu Petriș[5], Larisa Bianca Galea-Holhoș[4], Adrian Osiceanu[4], Mariana Tudoran[3], Bianca Neli Burtă[8], Radu Fodor[8]

1. *Department VII, Internal Medicine II, Discipline of Cardiology, University of Medicine and Pharmacy "Victor Babes" Timisoara, E. Murgu Square, Nr. 2, 300041 Timisoara, Romania.*
2. *Center of Molecular Research in Nephrology and Vascular Disease, Faculty of Medicine, University of Medicine and Pharmacy "Victor Babes" Timisoara, E. Murgu Square, Nr. 2, 300041 Timisoara, Romania.*
3. *County Emergency Hospital "Pius Brinzeu", L. Rebreanu Str., Nr. 156, 300041 Timisoara, Romania.*
4. *Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.*
5. *County Clinical Emergency Hospital of Oradea, 410087 Oradea, Romania.*
6. *Department of Anesthesiology and Intensive Care, Regional Institute of Gastroenterology and Hepatology "Prof. Octavian Fodor", 400162 Cluj-Napoca, Romania.*
7. *Department of Medical, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.*
8. *Doctoral School of Biomedical Sciences, University of Oradea, 410087 Oradea, Romania.*

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ABSTRACT

Mitral valve prolapse (MVP) has an incidence ranging from 2 to 3%. It is usually a benign condition, but it can be associated with an increased risk of ventricular arrhythmias (VA) leading to sudden cardiac death (SDC). Our study aimed to evidence to victims of SDC, the incidental presence of MVP, and the associated histological alterations. In patients with MVP, we assessed the increased risk for VA, by studying the Heart Rate Variability (HRV) and Heart Rate Turbulence (HRT). Firstly, in 2021, we conducted a morpho-pathological study on 225 victims of SDC, and concomitantly, a clinical study was performed on 50 patients with MVP who underwent 24 hours Holter monitoring. In the first study, we evidenced in 8 subjects, alterations of the mitral valve (MV) suggestive of MVP, and associated with fibrotic lesions in the vicinity of MV. The patients included in the clinical study were divided into two groups based on age, clinical particularities, and 2D-echocardiographic aspect: group A: 23 subjects younger than 40 years with myxomatous degeneration of the MV and group B, 27 elderly patients with MVP and associated cardiovascular pathology. In patients with MVP, 24-hour Holter monitoring may evidence alterations of HRV and HRT, frequently related to the severity of mitral regurgitation (MR), which could explain the increased risk for VA.

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Corresponding Author: Florica Voiță-Mekeres; Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. E-mail: mekeres_florina@yahoo.com.

Introduction

Mitral valve prolapse (MVP) represents a fairly common valvular anomaly of the mitral valve (MV) with a prevalence ranging from 2 to 3% [1-3]. It is induced by fibro-myxomatous degeneration with thickening and lengthening of the anterior and/or posterior MV leaflets, with their displacement into the left atrium (LA) during systole, associated with poor coaptation [1]. MVP can be associated with connective tissue diseases (CTD) or other cardiovascular (CV) pathologies [4-7]. In 40-50% of cases, there is a familial aggregation, suggesting the involvement of genetic factors [1, 4, 5]. There are two main aetiological forms of MVP: primary "non-syndromic" (mixomatous degeneration without identifiable fibroelastic or CTD) and secondary "syndromic" (associated with CTD such as Marfan, Loeys-Dietz, and Ehlers-Danlos syndrome, etc.) [1, 8].
Two-dimensional (2D) echocardiography is the most commonly employed method for the screening of MVP, the diagnosis being certified by the nonsymmetrical displacement of one or both leaflets above the plane of the mitral annulus, in a buckling appearance [9].
Commonly MVP represents a benign condition, but in some patients, it can be associated with ventricular arrhythmias (VA) or even sudden cardiac death (SCD) or it can result in severe mitral regurgitation (MR) and heart failure [4, 10, 11]. The risk of developing VA can be estimated on the 24-hour Holter monitoring and by analyzing the heart rate variability (HRV) and heart rate turbulence (HRT), both characterizing the status of the autonomic nervous system (ANS) [4, 5, 12]. These methods are used in various studies to estimate the sympathovagal imbalance in patients with CV pathologies and to predict an increased CV risk and morbidity [12-14]. The sympathovagal imbalance favors the onset of VA and increases the risk of SCD [5, 14, 15].
This study aims to evidence the increased risk for VA through the study of HRV and HRT on the 24-hour Holter monitoring, in patients with MVP assessed echocardiographically [16-18]. Another purpose is to document, in victims of SCD, the morpho-pathological changes associated with MVP.

Materials and Methods

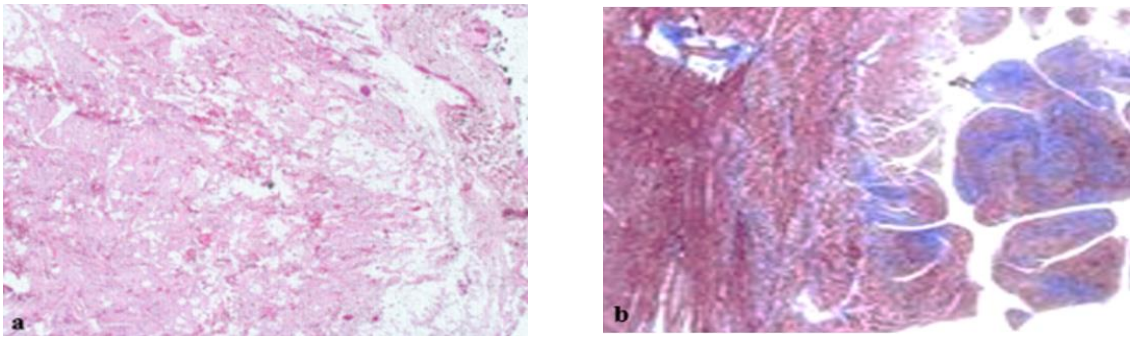
Morphopathological study: of all 225 victims of SCD examined during 2021 in the Forensic Department of our County, 29 subjects were under 40 years and 196 had ages between 40 and 75 years. In three cases of the first category and five of the second, the anatomopathological examination revealed alterations of MV leaflets, suggesting MVP. MV leaflets involvement, as well as the presence of endocardial fibrous plaques on the left ventricular (LV) postero-lateral, was studied on the collected hearts. Probes from leaflets, papillary muscles, and the affected adjacent endocardium, were collected and fixed in Formalin-solution. Sections 5 μm thick were stained with hematoxylin-eosin and examined by a skilled pathologist [17-20].
Study groups: based on age, clinical particularities, and 2D-echocardiographic assessment, fifty patients diagnosed with MVP were assigned to 2 groups: Group A: included 23 patients, 10 men and 13 women, aged between 18 and 39 years, diagnosed with MVP, of one or both leaflets, associated with MR of various severity. None of them was certainly diagnosed with Marfan syndrome. Group B: 27 patients, 14 men and 13 women, aged between 42 and 74 years, with MVP, mostly of the posterior leaflet, accompanied by MR were included in this group.
Cardiologic evaluation: after a rigorous physical examination, and 12-lead ECG, all patients were evaluated by 2-D echocardiography, all assessments being performed by the same skilled operator. MVP was certified by the evidence of an over 2 mm displacement of one or both leaflets of MV into LA during systole, taking on a buckling appearance, with a leaflet thickening > 5 mm during diastole in longitudinal long axis and apical 4-chamber views [9]. We also determined LV mass index (LVMI), and LA maximum volume index (LAVI) ejection fraction (EF) in the Simpson method. Doppler echocardiography was used to quantify the severity of MR [9].
All patients had 24-hour Holter monitoring, performed with a Holter Labtech Cardiospy device. We analyzed the presence and severity of VA. To analyze the obtained data we used the Nevrokard Long-Term aHLV (L-aHRV V.5.0.0.) program. Regarding HRV, which describes the spontaneous fluctuations in heart rate (HR) and normal RR intervals, we assessed the standard deviation of all normal to normal (NN) intervals (SDNN) in the time domain. Patients with SDNN values below 50 ms were classified as unhealthy, 50–100 ms had compromised health, and above 100 ms were healthy [14]. To determine HRT we included in our study only patients with at least 6 PVC. For HRT, which analyzes the sinus rhythm cycle length variation after isolated premature ventricular contractions (PVC), we determined the turbulence onset (TO) - early sinus acceleration after a PVC and the turbulence slope (TS) - late sinus deceleration following a PVC. In most studies, TO<0% and TS>2.5 ms/R-R interval are considered normal, but according to risk stratification studies, HRT can be divided into 3 categories: Category 0 - TO and TS are normal, category 1 – TO or TS is abnormal, category 2 - TO and TS are abnormal [14, 15].
Statistical methods: Data analysis was performed using SPSS v.25 (Statistical Package for the Social Sciences, Chicago, IL, USA). Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables were presented as frequency and percentages. The results of the normality test (Shapiro-Wilk) showed a non-Gaussian distribution, the reason why we continued to use nonparametric tests. To compare continuous variables between groups we applied the Mann–Whitney U test. To evaluate the relation between MR and HRT we used Spearman`s correlation test. A p-value of less than 0.05 was considered to indicate a statistically significant difference.
The study was approved by the Ethics Committee of our hospital (Nr. 4052/19.06.2020) and all patients signed a written informed consent.

Results and Discussion

Morphopathological Study

225 victims of SCD were examined in the Forensic Department of our County in 2021. In 3 out of 29 subjects aged under 40 years and in 5 of the 196 with ages between 40 and 75 years, the macroscopic examination of collected hearts revealed alterations of the MV suggestive of MVP and patchy fibrosis in the adjacent areas. In younger SCD victims with MVP, on gross examination, there was evidence of posterior (66%) or bileaflet (33%) myxomatous degeneration. Valvular leaflets were thickened, with elongated chordae. In the older SDC subjects with MVP, there was evidence of bileaflet involvement in 40% and only of the posterior leaflet in 60%. Regional thickening of the leaflets, with elongated, fibrotic chordae and fibrous plaques of the adjacent posterolateral wall was observed in all cases.

Histological examinations of the MV, evidenced in younger patients, myxomatous infiltration with mucopolysaccharide accumulation, **(Figure 1a)** while in the older ones, fibroelastic alterations prevailed. Collagen disruption and elastin fragmentation were present in both types. Overall, in 6 cases (75%), there was evidence of endo-myocardium alterations with patchy fibrosis **(Figure 1b)** of the posterior leaflet, adjacent free wall, and the top of the papillary muscle where some hypertrophied cardiomyocytes with dysmorphic and dissymmetric nuclei were also detected.



a) b)

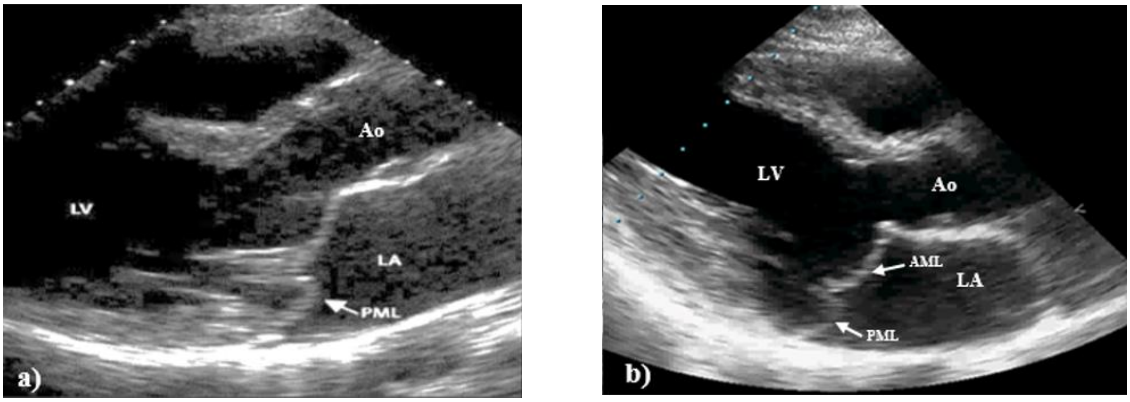
Figure 1. Aspects of histology of MVP evidencing myxoid infiltration of the MV (a) and pathy fibrosis of the postero-lateral wall and the papillary muscles (b)

Legend: a) myxoid degeneration of the MV with thickening and excessive amounts of basophilic myxomatous material in the valve; b) myocardial fibrosis of the LV postero-lateral wall and papillary muscle.

Table 1. Results of clinical data, 2D echocardiography, and 24-hour Holter monitoring

Clinical and laboratory data	Group A (n=23)	Group B (n=27)	*p*-value
Gender: men/women [a]	10/13	14/13	0.555
Age [b]	27 (21-34)	61 (52-68)	<0.001
Echocardiography:			
MVP of anterior leaflet [a]	2	3	0.951
MVP of the posterior leaflet [a]	12	15	0.811
MVP of both leaflets [a]	9	9	0.770
MR: Mild/Moderate/ Severe [a]	14/8/1	9/13/5	0.098
Hypo/a/dyskinesia [a]	-	21/6/4	-
LAVI [b]	33.2 (32.9-34.9)	37 (35.9-38)	<0.001
LVMI [b]	93 (92-112)	99.2 (95.6-117)	<0.001
EF (Simpson) [b]	65 (62-69)	51 (49-52)	<0.001
24-hour ECG Holter monitoring:			
Mean HR [b]	76 (75-78)	63 (62-65)	<0.001
PVC – isolated [a]	23	27	1
- systematized [a]	8	13	0.167
- unsustained/sustained VT [a]	1	6	0.199
SDNN [b]	107 (102-109)	97 (52-102)	<0.001
HRT Category 0 [a]	20	7	<0.001
Category 1 [a]	2	11	0.011
Category 2 [a]	1	9	0.013

Legend: BMI –body mass index; MVP –mitral valve prolapse; MR –mitral regurgitation; LAVI –left atrial volume index; LVMI – left ventricular mass index; EF –ejection fraction; HR –heart rate; PVC –premature ventricular contractions; VT –ventricular tachycardia; SDNN – standard deviation of normal-normal RR intervals; HRT – heart rate turbulence.



a) b)

Figure 2. a) 2D echocardiography of posterior leaflet prolapse and b) bileaflet prolapse
Legend: LA= left atrium; LV= left ventricle; Ao=aorta; PML= posterior mitral leaflet; AML=anterior mitral leaflet

Clinical Study

Group A included 23 patients, 10 men, and 13 women, with a median age of 27 (21-34) years, diagnosed with MVP using 2D echocardiography, **Figure 2**. Their clinical and laboratory data are illustrated in **Table 1**. In most cases (52.17%) the prolapse of the posterior leaflet prevailed **Figure 2a**, followed by the bileaflet form, **Figure 2b**. The associated MR was mild in most cases (60.83%). In this group, 20 patients had SDNN over 100 ms with HRT category 0. They had mild MR and only 6 had moderate MR. 2 patients had SDNN between 50 to 100 ms with HRT category 1, both with moderate MR. One patient had SDNN under 50 ms, HRT category 2, and severe MR due to bileaflet MVP. The statistical analysis by using Spearman correlation evidenced a moderate correlation r=0.553; p=0.006 between HRT and the severity of MR.

Group B included 27 patients, 14 men and 13 women with a median age of 61 (52-68) years, diagnosed with MVP. 22 of them had a history of other CV diseases. As in group A, MVP of the posterior valve prevailed, followed by the bileaflet form. MR was more important: 66.66% of the patients had moderate or severe MR. Median LAVI and LVMI were significantly higher and EF lower than those registered in group A, ($p<0.001$), see **Table 1**. In this group, 9 patients had normal SDNN, and 4 of them, 2 with moderate MR, had HRT category 1. 12 patients had SDNN between 50 and 100 ms, 2 with HRT category 0, 7 with category 1 and 3 with category 2. 2 had mild MR, 9 moderate and 1 severe form. The last 6 subjects from group B had SDNN under 50 ms and HRT category 2, 4 of them having severe MR. In group B we evidenced a strong correlation between HRT and the severity of MR (r=0.777; p=0.001) by using Spearman correlation.

In this study, we analyzed the results of autopsies performed in the Forensic Institute of our county on 225 subjects deceased by SCD in 2021. In 8 cases (3.55%), MVP was identified. Histological examinations conducted on specimens collected from these hearts, evidenced in younger patients myxomatous degeneration, mostly of the middle scallop, as in the classic Barlow's disease, while in the older subjects, fibroelastic alterations with elongated and even ruptured chordae prevailed, associated far more frequently with fibrotic plaques.

As described in the medical literature, surgically excised MV from patients with MVP and significant MR, have an increased surface area with enlarged mitral annulus and thin, elongated, or even ruptured chordae tendineae [1, 5]. MVP with diffusely thickened leaflets of over 5 mm is currently referred to as Barlow's valves, whereas regional MV thickenings of under 5 mm are considered fibroelastic deficiency. To date, it is not clear whether these two entities are genetically different or represent a different spectrum of abnormalities of the same disease (or both). Our results of the histological examinations in SCD victims with MVP were similar to those described in classic, histological studies evidencing myxomatous degeneration with mucopolysaccharide infiltration, collagen disruption, and elastin fragmentation of the MV leaflets and chordaes tendineae [1]. Other effects of MVP include leaflets fibrosis and ventricular friction lesions which could be responsible for the occurrence of VA [21, 22]. It has been speculated that in MVP, papillary muscles are altered by repetitive traction exerted by the prolapsing leaflets [5] which has been shown experimentally to lower the threshold for arrhythmias [21, 22]. Although more frequent VA on 24-hour ambulatory Holter monitoring has been demonstrated in MVP patients with scarring of the papillary muscles, its clinical significance remains to be established [21, 23].

Our clinical study was conducted on fifty patients with MVP confirmed using 2D echocardiography [9]. Posterior leaflet MVP prevailed, followed by the bi-leaflets form, but anterior leaflet prolapse occurred seldom. All patients had MR of various degrees.

The diagnosis of MVP represents a dilemma in echocardiography. There are two basic forms of MVP: the classic one, diagnosed in younger patients, is associated with myxomatous leaflets. The second, which occurs in the elderly, is often associated with coronary artery disease and progressive MR. MVP, observed only in apical 4-chamber view, often represents a false positive diagnosis due to the saddle-shaped MV annulus, a complex 3D structure, with multiple scallops [9]. The introduction of 3D echocardiography in clinical practice provides more accurate information on the MV structure and function and enables the precise definition of each scallop.

Regarding HRV and HRT analysis in our study, in group A only 2 patients with moderate MR had slightly reduced SDNN and one, with severe MR, had severely reduced SDNN with HRT category 2. In group B, SDNN values were pathological in 66.66% of patients. The HRT analysis evidenced pathological aspects in 92.59% of cases, especially in those with moderate or severe MR where the statistical analysis evidenced strong correlations between HRT and the severity of MR ($r=0.777$; $p<0.001$). Overall, referring to all patients, we documented strong correlations between HRT and the severity of MR ($r=0.715$; $p=0.001$). These data sustain the hypothesis that patients with MVP have ANS imbalance characterized by increased sympathetic outflow [5, 6].

It has to be mentioned that this study was performed during the COVID-19 pandemic, and although we tried to include mostly patients already diagnosed with MVP before 2020, many of them could have suffered a SARS-CoV-2 virus infection which, besides effects on various organs and systems [24, 25] is known to impact the ANV thus producing alteration of HRV and HRT.

HRV and HRT alterations in patients with MVP and MR represent a subject of debate in many studies. Several authors described patients with MVP enhanced sympathetic and reduced parasympathetic activity with depressed HRV [14, 15]. Turcher Y highlighted the relation between an increased risk for VA and the severity of MR [26]. On the other hand, Van der Wall failed to evidence significant relations between HRT, HRV, and the incidence of VA [12]. Other studies revealed alterations of HRT in patients with MVP compared to controls [5, 10, 27-30]. This finding is likely related to underlying ANS dysfunction rather than to hemodynamic alterations. In our study, HRT alterations evidenced in group B could be explained by the fact that these patients were older, some of them suffering from coronary artery disease and having decreased EF. It should be considered that although MVP is not such an invalidating disease, especially in young patients, the increased incidence of arrhythmias and even this threat, impact the mental health of these patients rendering them prone to anxiety/depression, often requiring psychiatric evaluation [31, 32].

Conclusion

In patients with MVP, the susceptibility to develop VA seems to be related to the sympathovagal imbalance and can be estimated by the study of HRV and HRT. These parameters are related to the severity of MR. The susceptibility to developing VA appears to be associated with the progression of fibrosis lesions in the MV proximity.

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Conflict of interest: None

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Ethics statement: The study was approved by the Ethics Committee of our hospital (Nr. 4052/19.06.2020) and all patients signed a written informed consent.

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