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# Mitral valve prolapse syndrome and MASS phenotype: Stability of aortic dilatation but progression of mitral valve prolapse☆

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ABSTRACT

*Background:* Mitral valve prolapse syndrome (MVPS) and MASS phenotype (MASS) are Marfan-like syndromes that exhibit aortic dilatation and mitral valve prolapse. Unlike in Marfan syndrome (MFS), the presence of ectopia lentis and aortic aneurysm preclude diagnosis of MVPS and MASS. However, it is unclear whether aortic dilatation and mitral valve prolapse remain stable in MVPS or MASS or whether they progress like in MFS.
*Methods:* This retrospective longitudinal observational study examines clinical characteristics and long-term prognosis of 44 adults with MVPS or MASS (18 men, 26 women aged 38 ± 17 years) as compared with 81 adults with Marfan syndrome (MFS) with similar age and sex distribution. The age at final contact was 42 ± 15 years with mean follow-up of 66 ± 49 months.
*Results:* At baseline, ectopia lentis and aortic sinus aneurysm were absent in MVPS and MASS, and systemic scores defined by the revised Ghent nosology were lower than in MFS (all $P < .001$). Unlike in MFS, no individual with MVPS and MASS developed aortic complications ($P < .001$). In contrast, the incidence of endocarditis ($P = .292$), heart failure ($P = .644$), and mitral valve surgery ($P = .140$) was similar in all syndromes. Cox regression analysis identified increased LV end-diastolic ($P = .013$), moderate MVR ($P = .019$) and flail MV leaflet ($P = .017$) as independent predictors of mitral valve surgery.
*Conclusions:* The study provides evidence that MVPS and MASS are Marfan-like syndromes with stability of aortic dilatation but with progression of mitral valve prolapse. Echocardiographic characteristics of mitral valve disease rather than the type of syndrome, predict clinical progression of mitral valve prolapse.


## 1. Introduction

Modern echocardiographic criteria identify mitral valve (MV) prolapse (MVP) with systolic prolapse >2 mm of MV leaflets, and with leaflet thickening ≥5 mm during diastole. MVP is non-classic with isolated presence of leaflet prolapse and classic when combined with leaflet thickening [1]. Classic and non-classic MVP together have a prevalence of 2.4% in the general population [1].

Some individuals with MVP develop severe MV regurgitation, endocarditis, heart failure, and sudden cardiac death [2]. MVP may occur as a familial, and non-familial trait and MVP can manifest with syndromic or non-syndromic phenotype [3]. The etiology of MVP is largely unknown. Several findings argue for involvement of genetic factors in the pathogenesis of MVP: (1) some families with MVP exhibit X-linked or autosomal dominant inheritance with incomplete penetrance [3], (2) genetic studies showed linkage of MVP to chromosomes 3q31.3–q32.1, 11p15.4, and 16p12.11–p11.2, (3) some MVP phenotypes are caused by mutations in the X-linked filamin A gene (*FLNA*) [3,4], or in *DCHS1* [5], and (4) MVP is an established cardiovascular feature of several genetic aortic disorders including Marfan syndrome (MFS), Loeys–Dietz syndrome, aneurysm osteoarthritis syndrome, and thoracic aortic aneurysms caused by mutations in the *TGFB2* and *SMAD3* genes [6]. In this study we examined MVP in Marfan-like syndromes comprising MVP syndrome (MVPS) and MASS phenotype (MASS).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Early descriptions of MVPS suggested atypical chest pain, exertional dyspnea, palpitations, syncope, anxiety, low blood pressure, lean body stature, and electrocardiographic repolarization abnormalities as typical features of MVPS [2], but of these only leaner body mass was confirmed in population-based cohorts [2,7]. Today, the revised version (Ghent-2) [8] of the initial Ghent nosology (Ghent-1) [9,10] defines MVPS as MVP with Marfan-like features including pectus excavatum, scoliosis and arachnodactyly, but with a systemic score on the Ghent-2 nosology <5 points [8]. The Ghent-2 systemic score considers 13 manifestations according to their diagnostic accuracy for MFS comprising MVP, myopia, skeletal manifestations, pneumothorax, dural ectasia, and skin striae. In addition, diagnosis of MVPS requires exclusion of aortic root aneurysm Z-scores ≥2 and of ectopia lentis [8].

In 1989 Glesby and Pyeritz suggested the acronym "MASS" to describe phenotypes involving MV, aorta, skeleton, and skin [11]. They suggested that individuals with the exclusion of ectopia lentis, with only mild dilatation of the aortic root and with Marfan-like manifestations including MVP, skeletal features, and skin striae should be diagnosed as having MASS [11]. In 1996 the Ghent-1 nosology revised MASS criteria as presence of myopia, MVP, mild aortic dilatation, skin striae, and minor skeletal involvement, where diagnosis required involvement of ≥2 different organ systems [9]. Similar to MVPS, the current Ghent-2 nosology redefined MASS with the presence of MVP and some Marfan-like clinical features and with exclusion of aortic root aneurysm (≥2 Z-scores) and of ectopia lentis. In contrast to MVPS the definition of MASS requires a systemic score ≥5 points. The etiology of MASS remains unknown, although some causative fibrillin-1 (*FBN1*) mutations presented with MASS phenotype [12]. *FBN1* mutations usually cause MFS which carries a high risk for rupture and dissection of the aorta. Some authors consider MASS as the mild end of a continuous spectrum of Marfan-like syndromes [13]. However, detection of a causative *FBN1* mutation in MASS raised concerns about MASS to evolve into outright MFS and overt dissection or rupture of the aorta [8,14].

Today, there is only scarce clinical data on MVPS [15–17] and MASS [11,12,14,18–21], and there is no study to assess MVPS or MASS with recent Ghent-2 criteria. Moreover, prognosis of MVP and aortic disease in MVPS and MASS has not been described. Hence, the Hamburg and Ghent Marfan centers joined to perform a retrospective longitudinal, observational study with the aim to characterize the clinical features of these entities by applying the current Ghent-2 criteria. Furthermore we studied the long-term outcomes of cardiovascular manifestations of MVPS and MASS in comparison with MFS. We wanted to test whether MVPS and MASS remained unaffected by aortic root complications, and we aimed to examine whether MVP evolved with similar severity as known in MFS, where MVP tends to be progressive [22–24].

## 2. Methods

### 2.1. Patients

We screened patient records for individuals aged 18 years or older who exhibited MVP diagnosed in MVPS or in MASS, and we compared these with individuals of the same age who exhibited MVP related to MFS. We identified a total of 44 adults with MVPS or MASS of whom 18 were men and 26 were women at a mean age of 38 ± 17 years (range 18–70 years), and 81 adults with MFS, including 34 men and 47 women at a mean age of 35 ± 12 years (range 18–67 years). We identified 80 of these patients in Hamburg and 45 patients in Ghent.

We applied Ghent-2 criteria to establish the final diagnosis of MVPS, MASS and MFS [8]. In brief, MVPS was present with MVP, exclusion of aortic root dilatation with Z-scores ≥2, ectopia lentis, and exclusion of a systemic score ≥5 points. Similarly, MASS was present with MVP, exclusion of aortic root dilatation ≥2 Z-scores and ectopia lentis, but with a systemic score ≥5 points including at least one skeletal feature. MFS was confirmed, first in the absence of a family history of MFS, with aortic root dilatation (Z-scores ≥2) and ectopia lentis, or with systemic score ≥7 points, or with ectopia lentis and a *FBN1* mutation known to cause aortic dilatation, and second, in the presence of a family history, with ectopia lentis, or with systemic score ≥7 points, or with aortic root dilatation (Z-scores ≥2) [8]. All individuals with MFS fulfilled clinical criteria and harbored a causative *FBN1* mutation [8]. We verified the diagnosis of MVPS and MASS clinically in all individuals at the age of >20 years [8], and we did not find a causative *FBN1* mutation in all these individuals. As Ghent-2 recommends, we diagnosed MVP with the presence of ≥1 of the echocardiographic standard criteria as specified below [8,25].

### 2.2. Genetic analysis

We extracted DNA from EDTA blood samples using standard procedures, and amplified the coding region and flanking intronic sequences including 20 nucleotides of the introns at each acceptor (positions −1 to −20) and donor splice site (positions +1 to +20) of the *FBN1*, (NM 000138.4), *TGFBR1* (NM 004612.2) and *TGFBR2* (NM 001024847.2) genes by PCR in all patients. We performed Sanger sequencing of the PCR products with an ABI PRISM 310 Genetic analyzer using the ABI

**Table 1**
Baseline characteristics in 125 adults with various syndromic forms of mitral valve prolapse.

| Variable[a] | MVPS (N = 29) | MASS (N = 15) | MFS (N = 81) | P[b] |
|---|---|---|---|---|
| Age at initial evaluation (years) | 42 ± 19 | 30 ± 11 | 35 ± 12 | .093 |
| Male gender | 14 (48%) | 4 (27%) | 34 (42%) | .399 |
| Total cholesterol (mg/dl) | 194 ± 39 | 207 ± 47 | 187 ± 40 | .366 |
| HDL cholesterol (mg/dl) | 58 ± 15 | 74 ± 22 | 55 ± 16 | .042 |
| LDL cholesterol (mg/dl) | 113 ± 27 | 117 ± 31 | 107 ± 36 | .406 |
| Systolic blood pressure (mm Hg) | 132 ± 17 | 125 ± 16 | 126 ± 16 | .302 |
| Diastolic blood pressure (mm Hg) | 75 ± 11 | 73 ± 14 | 73 ± 10 | .521 |
| BAB medication | 8 (28%) | 2 (13%) | 40 (49%) | .009 |
| ACEi or ARB medication | 3 (10%) | 0 | 17 (21%) | .087 |
| Previous ischemic neurologic event | 2 (7%) | 0 | 4 (5%) | .687 |
| Ectopia lentis | 0 | 0 | 38 (47%) | <.001 |
| Systemic score (points) | 1.1 ± 1.3 | 7.2 ± 3 | 7.3 ± 3.5 | <.001 |
| Aortic sinus diameter (cm) | 3 ± .4 | 2.9 ± .4 | 4.5 ± 3 | <.001 |
| Aortic sinus Z-score | −.8 ± 1.3 | −.8 ± 2.1 | 3.7 ± 2.9 | <.001 |
| LV ejection fraction (%) | 59 ± 11 | 58 ± 8 | 57 ± 11 | .900 |
| Indexed LVESD (mm/m$^2$) | 17 ± 4 | 18 ± 3 | 17 ± 4 | .788 |
| Indexed LVEDD (mm/m$^2$) | 27 ± 4 | 27 ± 3 | 27 ± 4 | .966 |
| Indexed left atrial diameter (mm/m$^2$) | 21 ± 6 | 18 ± 3 | 19 ± 4 | .240 |
| Anterior MV leaflet prolapse[c] | 22/28 (79%) | 11/13 (85%) | 75/80 (94%) | .060 |
| Posterior MV leaflet prolapse[c] | 15/28 (54%) | 2/13 (15%) | 53/80 (66%) | .002 |
| Bileaflet MVP[c] | 11/28 (39%) | 1/13 (8%) | 48/80 (60%) | <.001 |
| MV bileaflet thickening | 9/26 (35%) | 4/13 (31%) | 14/80 (18%) | .151 |
| Moderate degree of MVR | 11 (38%) | 4 (27%) | 13 (16%) | .049 |
| Flail MV leaflet | 3 (10%) | 0 | 4 (5%) | .488 |
| Tricuspid valve prolapse | 3/27 (11%) | 1/13 (8%) | 26/79 (33%) | .022 |
| NT-proBNP (pg/ml) | 67 ± 63 (N = 7) | 100 ± 100 (N = 7) | 842 ± 2249 (N = 48) | .003 |

ACEi identifies angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BAB, beta-adrenergic blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; MASS, MASS phenotype; MV, mitral valve; MVR, mitral valve regurgitation; MVPS, mitral valve prolapse syndrome; MFS, Marfan syndrome; np, not performed; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

[a] Continuous data are presented as mean ± standard deviation.

[b] Kruskal–Wallis test for continuous data and the generalized Fisher's exact test for nominal and categorical data.

[c] We excluded 1 individual with MVPS and MFS, respectively, and 2 individuals with MASS because in these documentations MVP was available without original echocardiographic documentation; we included 2 individuals with MVPS and 1 with MASS, who had original echocardiographic documentation which described buckling of a single MV leaflet according to Freed without specification of MV leaflet. We considered mono-leaflet MVP in these 3 individuals, but we counted prolapse as absent in both the anterior and the posterior MV leaflet.