

# Mitral valve prolapse: where is the missing link?

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Mitral valve prolapse (MVP), is the most common cause of primary mitral regurgitation but remains the subject of debates and gaps of knowledge regarding diagnostic criteria, prevalence and outcome. Diagnostically, the debate appeared settled in the 1980's after the seminal description by Levine *et al.* of mitral annulus saddle shape and its influence on MVP diagnosis by echocardiography (1). MVP has since been defined by systolic override of one or both mitral leaflets  $\geq 2$  mm above the mitral annulus plane in parasternal long axis or apical 3 chambers view. Prevalence of MVP, based on those criteria, subsequently was estimated around 2.4% of the general population (2). However, as with any single, absolute parameter-based clinical threshold, potential neglect of less clearly defined mitral valve abnormalities, not reaching the 2 mm threshold but suggestive of MVP (thickening and/or billowing), may be a concern. These "incomplete" patterns were classified as physiologic variants of the normal mitral valve, likely not associated with adverse outcomes but were not the focus of specific studies. This "normality" notion was recently challenged in genetic studies that demonstrated the presence of these subtle abnormalities in carriers of mutations linked to MVP (3). Thus, there has been a regain of interest for these "forme fruste" phenotypes, which have been labeled as non-diagnostic forms of MVP (NDM). Presence of NDM in the context of familial MVP suggested possible pathological continuity between NDM and MVP, and NDM as a missing link between the normal valve and the fully characterized MVP. Previous work using the systematic echocardiographic examination of subjects within the Framingham cohort separated NDM patterns (4) in two categories: abnormal anterior coaptation (AAC) and minimal systolic displacement (MSD). However, NDM presence could not be extrapolated to clinical significance and long-term echocardiographic outcomes remained undefined. In the 26 April 2016 issue

of Circulation, Delling *et al.* (5) provide further insights on echocardiographic progression of patients presenting with NDM or MVP from the 5th Framingham cohort and compared them to a reference population issued from the same cohort. After a median follow up of one decade, they observed that 80% (8 out of 10) of patients with AAC and 24% (12 out of 50) of patients with MSD had evolved to full MVP diagnostic criteria while only 1.4% (2 out of 138) of the referent population evolved to MVP.

## NDM: the missing link between a normal mitral valve and MVP?

MVP is most generally diagnosed in adults, often in their 5th–6th decade and is rare among children (6). Its development is linked to the process of extracellular matrix "maintenance" and may involve excessive catabolism and defective remodeling of leaflet's extracellular matrix causing myxomatous degeneration of the mitral valve (7). Therefore, due to the progressivity of the condition, the MVP phenotype appears with age and it appears likely that an intermediate feature exists in transition from a normal mitral valve to a complete MVP. This work adds new evidence that NDM is this intermediate stage which can sometimes secondly evolve to complete MVP. NDM is not a marker of poor prognosis as the evolution to MVP is both uncertain and slow but these incomplete patterns should be noted and followed, even episodically.

It is essential that these observations be confirmed, as the subjects were retrospectively identified among a preselected patient-group tagged as having possible MVP. Definite criteria should be tested as reproducible lest we induce the same fear and anxiety that our previous overestimation of MVP prevalence had caused. Also, these observations are made on very small samples of subjects and while a

theoretical intermediary state between a normal valve and MVP is logical, no clinical implication can be drawn.

### NDM: precursor of all types of MVP?

MVP is heterogeneous, representing a range of pathological conditions, distributed into two main categories: Barlow's disease, characterized by large tissue excess, multi-segment prolapse and often diffuse mitral tissue thickening; and the fibroelastic deficiency with prolapse or flail of a limited portion of the mitral leaflets, most commonly P2, when the remaining part of the valve has a normal appearance. Classically, the evolution is different between these two entities with more aggressive progression toward severe mitral regurgitation via ruptured chord occurrence for fibro elastic deficiency, versus more progressive evolution for Barlow's disease. It is not known whether these two forms are different stages of the same disease or if they are two different pathologies with two distinct progression modes. New data from 3D echocardiography (8) support the hypothesis that fibroelastic deficiency and Barlow's disease presenting with an array of different valvular mechanics are different "diseases". The work from Delling *et al.* does not address this issue and did not differentiate fibroelastic deficiency from Barlow's disease in the evolution of NDM. It would be interesting to investigate whether NDM evolve preferentially toward one or the other phenotype.

### Outcomes of MVP vs. NDM

The second part of the work from Delling *et al.* focused on clinical outcome of MVP and of NDM. Patients presenting with MVP at baseline often (25%) evolved toward moderate or severe MR or mitral surgery. This confirms previous studies (9,10) whereby progression involved not just the MVP but its main consequence: MR, with aggravation of mitral regurgitation over time quite prevalent. A potentially "similar" clinical outcome (death and cardiovascular event) reported by Delling among NDM, MVP and referent population should be discounted due to very limited number of patients. More work needs to be done to define, as reliably as possible, the degree of mitral regurgitation at baseline and follow-up; and to test the potential relationship between mitral morphology and mitral regurgitation progression rate.

### Conclusions

This population longitudinal follow up of patients

presenting with NDM and MVP, shows the trend for progression of mitral lesions, so that NDM likely represents a missing link in the phenotypic evolution of MVP. Therefore, clinical and research attention should be paid to these phenotypes. Both should be part of genetic studies of MVP. Clinically, while NDM may progress to MVP, its clinical significance remains unclear. It is reasonable to prospectively note these NDM cases once precise definitions have been validated in larger samples, but we should not lose sight that the main determinant of clinical outcome of patients with degenerative mitral valve disease is not (or little) valve morphology but the severity, preferably quantified, of its consequence: mitral regurgitation.

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*Comment on:* Delling FN, Rong J, Larson MG, *et al.* Evolution of Mitral Valve Prolapse: Insights From the Framingham Heart Study. *Circulation* 2016;133:1688-95.

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