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SCIENTIFIC EDITORIAL

Mitral regurgitation due to mitral valve prolapse: Four decades of controversies



Prolapsus valvulaire mitral : quatre décennies de controverses

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Diagnostic criteria and prevalence of mitral valve prolapse

After the first clinical definition of mitral valve prolapse (MVP), based on the typical click and murmur syndrome [1], echocardiography in the mid-1970s introduced a new era of non-invasive diagnosis, but created ambiguity and debate. Using the initial diagnostic criteria, the prevalence of MVP was reported to be as high as 5% in the general population and 17% in some population groups [2]. One decade later, three-dimensional work [3] furthered our understanding of mitral annulus morphology and the contribution of its saddle shape to echocardiographical patterns previously attributed to MVP. Mitral leaflets can appear to protrude in the apical four-chamber view without actual MVP, the echocardiographical diagnosis of which is currently based upon a leaflet overshoot of ≥ 2 mm in long-axis views only [4]. Whether the current definition should be restricted to protrusion of the coaptation line, as emphasized in European countries (particularly France), or applied equally to posterior displacement of either the tip or the body of mitral leaflets, is not a critical issue, as it does not affect outcome, which is determined by the amount of mitral regurgitation (MR) associated with MVP [5]. This clarification of diagnostic criteria was crucial for redefining the prevalence of MVP in the population. Although considerably lower than with the older criteria, the prevalence of MVP remains high (0.6–2.4%) [4]; MVP is therefore estimated to affect more than 150 million subjects worldwide, which highlights the importance of defining its prognosis comprehensively.

Abbreviations: EF, ejection fraction; LV, left ventricular; MIDA, Mitral Regurgitation International Database; MR, mitral regurgitation; MVP, mitral valve prolapse.

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Outcome of mitral valve prolapse: benign or severe?

The clinical outcome of MVP has been another source of passionate controversy and the disease has been considered successively as either severe [6,7] or uniformly benign [4]. This latter statement was contradicted by surgical and pathological series that undeniably established MVP as the leading cause of severe MR requiring surgery in Western countries [8].

Methodological issues related to change in diagnostic criteria as mentioned above and selection bias in the referral of either the most severe patients in tertiary care centers [6,7] or, conversely, the healthiest asymptomatic volunteers [4], explain parts of these divergent views. Data based on all community patients routinely diagnosed with asymptomatic MVP in their primary care hospital using modern criteria helped to reconcile these discordances. The data highlighted the heterogeneity of the disease, the prognosis of which encompasses a wide and continuous clinical spectrum, from extremely benign to severe, depending on the severity of mitral regurgitation at diagnosis [5]. Approximately half of MVP patients incur high rates of cardiovascular complications, including mortality, when significant MR and/or left ventricular (LV) dysfunction is present, whereas half (i.e. those with no MR and normal LV function) have an excellent outcome.

In addition, these community-based analyses allowed clarification of the disputed role of MVP in the occurrence of cryptogenic stroke in young patients, which varied over 20 years from strong [9] to absent [10], mainly in case-control studies. Comparison of observed rates of ischemic stroke in community MVP patients with those expected in the same community showed actual excess risk of ischemic events attached to MVP, but confined to elderly patients and not observed in the young. Indeed, older age, mitral leaflet thickening, atrial fibrillation and mitral surgery were the main risk factors for neurological complications, putting MR again at the centre of the physiology of MVP complications, through its atrial consequences and the need for cardiac surgery, both of which increase with ageing [11].

Outcome of severe regurgitation due to mitral valve prolapse: excess mortality or benign? Impact of ageing on outcome

These community-based data were in total agreement with other series focusing on subsets of patients with severe MR due to flail leaflet referred to tertiary surgical centers. These studies consistently reported excess mortality under conservative management compared with what was expected, even in asymptomatic patients [12], and high morbidity, including atrial fibrillation and congestive heart failure, both in the USA [12,13] and Europe [14]. Ten years after the diagnosis of severe MR due to MVP, 90% of all patients were dead or had been operated on for severe symptoms [13,14], highlighting the unavoidable nature of surgery in the course of the disease. Determinants of adverse outcome under conservative management included severe symptoms, decreased LV ejection fraction

(EF), increased LV end-systolic diameter, atrial fibrillation, left atrial remodeling, pulmonary artery hypertension and effective regurgitant orifice area [12], which are therefore considered as surgical signals [15]. However, in 2006, a single tertiary care centre study reported excellent outcome in 132 asymptomatic patients with severe MR due to MVP, disputing the severity of the disease while asymptomatic [16]. Of note, besides the small sample size, MR was not quantified, only 43% of all patients had flail leaflet and importantly the mean age of the study population was 55 years (i.e. > 10 years younger than in previous community-based studies [5]).

A recent study from the Mitral Regurgitation International Database (MIDA) aimed to further understand the origin of these divergent perceptions [17]. The MIDA registry provides a large amount of multicenter data collected in five centers in Europe and one in the USA, by enrolling in routine practice patients with flail mitral leaflet used as a model of pure severe organic MR [14,18]. This study focused on the clinical outcome under conservative management of 862 patients with flail leaflet, who were mostly asymptomatic, according to age at diagnosis. Given the normal increase in complications with ageing and in order to analyze the impact of age per se on tolerance of severe MR, the study compared mortality and morbidity rates with those expected in a general population of similar age [17]. Despite similar echocardiographical characteristics of the mitral lesions and similar indexed LV diameters suggesting similar volume overload in young patients as in older, patients aged ≥ 65 years displayed significantly higher mortality rates vs expected mortality in the general population, whereas this difference was not significant in younger patients. This observation favors the hypothesis of decreased tolerance of regurgitation in the elderly and offers a plausible explanation for lower observed mortality in young study populations [16]. Impaired intrinsic myocardial anatomical and pathological properties of the normal aged heart could result in reduced LV adaptation to volume overload in older patients. Nevertheless, although rates of heart failure and atrial fibrillation increased with age at diagnosis, comparison with expected rates revealed excess rates of both events in the youngest age group, just as in the oldest age group. Such an observation in young patients with low absolute numbers of events required a large population and could easily be missed by smaller samples [16].

In summary, these data support the hypothesis that excess risk of serious non-fatal complications can be expected in young patients, just as in older patients, despite the absence of symptoms and normal EF, which ultimately leads to a delayed excess mortality becoming significant with ageing.

Early surgery or watchful waiting?

The conclusion of the authors of the unique study that reported a benign outcome [16] was that asymptomatic patients with severe MR could be "safely followed until either symptoms occur or currently recommended cutoff values for LV size, LV function or pulmonary hypertension". This so-called watchful waiting attitude feeds another

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