Pulmonary hypertension: a long-term risk stratifier in primary mitral regurgitation

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The prognostic significance of pulmonary hypertension (PH) in primary mitral regurgitation (MR)

Primary MR is a degenerative disease whose rates are continuously increasing within the elderly population. It is a progressive disease in which chronic volume overloading causes myocardial damage, heart failure and even death; however, the correction of MR is curative (1). The ideal timing of surgical intervention in primary MR is critical but still challenging. The degree of dyspnoea, amount of regurgitant volume, signs of left ventricular (LV) decompensation, and complications of atrial fibrillation and PH are considered when deciding the timing of the intervention. PH is a negative prognostic factor in various heart diseases, including primary MR (2). With PH in primary MR, more severe dyspnoea, higher operation-related and long-term mortality and more frequent persistent PH after surgery are associated (3-6).

Mentias *et al*. (7) recently published an impressive study on the impact of resting PH on long-term outcomes in patients with primary MR. This was a retrospective observational study that evaluated 1,318 patients with primary degenerative MR ≥3 with LV ejection fractions ≥60%. Patients were not sick, with low STS scores of 4±1%. Concomitant aortic valve disease and significant comorbidity precluding mitral valve (MV) surgery were excluded. During a mean follow-up of 7±2 years, MV surgery was performed in 86% of the cohort, and all-cause death occurred in 10%. Preoperative resting systolic pulmonary arterial pressure (SPAP) was independently associated with mortality, whereas MV surgery was associated with improved survival. The effect of SPAP was progressive, in which values ≥35 mmHg were associated with higher mortality. The study is remarkable for several reasons. First, it confirmed the prognostic significance of Doppler echocardiography-derived resting SPAP in primary MR. Second, a diagnostic threshold of significant PH was suggested, but an SPAP ≥35 mmHg was far less than what had been expected. Third, MV surgery showed a long-term survival benefit in primary MR patients with low surgical risk.

Pulmonary vascular pressure as a severity index of MR

Significant PH is usually defined as an SPAP >50 mmHg. However, the dichotomous determination of PH by a specific value is arbitrary, as SPAP is a continuous variable in the pulmonary vasculature. The impact on long-term mortality after MR surgery appeared to be <50 mmHg, and higher mortality was observed with higher SPAP (3). The present study by Mentias *et al*. again showed the prognostic

impact of SPAP was progressive from 35 mmHg (7). In the severity spectrum of primary MR, PH can be considered as a general haemodynamic phenomenon rather than a specific complication. The probable threshold indicating permanent pulmonary vascular remodelling appears to be around an SPAP of 35 mmHg.

Despite its critical importance, decision making for surgical timing in primary MR is not easy. LV dysfunction can progress without symptoms, the ejection fraction is often not relevant to LV systolic function, and MR severity is highly variable according to loading conditions. As the measurement of SPAP is more accurate and reproducible than varying MR severity even during exercise, assessing PH can compensate the limitation to risk stratification in primary MR (8).

Although echocardiography has the advantage of non-invasiveness, it also has critical limitations to provide the exact SPAP value matching with invasive catheterization. Pressure values are calculated from flow velocity using the Bernoulli equation with several haemodynamic assumptions in echocardiography (9). Despite such limitations, echocardiography-derived SPAP estimates have proven their prognostic relevance in many studies.

The primary determinant of PH in MR is increased left atrial pressure, which can be related to MR itself, or systolic or diastolic LV dysfunction. The backward elevation of pulmonary venous congestion by increased left atrial pressure leads to a passive increase in SPAP as typical group 2 PH related to left heart diseases (2,10). In addition, the repetitive and chronic elevation of passive pulmonary venous and arterial pressure would lead to pulmonary vascular remodelling. Reactive vasoconstriction can further elevate pulmonary vascular resistance, where a high SPAP beyond that expected from left atrial pressure occurs by group 1 pulmonary arterial hypertension-like mechanisms (11,12).

Mechanism of PH at rest and during exercise in primary MR

In asymptomatic patients with primary MR, the prevalence of PH is 9–20% at rest but reaches up to 46–58% during exercise (4,6,13). Because of the dynamic nature, MR severity can be varying according to loading conditions. Dynamic MR is the major determinant of exercise-induced PH (8). During exercise, MR and left atrial pressure can increase abruptly to exceed the left atrial compliance and pulmonary vascular recruitment and PH can develop (13).

The haemodynamic mechanism of dynamic MR is complex. MV geometry as well as volume overload may contribute to dynamic increase of MR during exercise. In primary degenerative MR, the MV apparatus undergoes remodelling such as dilated annular diameter, reduced annular height and flattening of annular saddle shape (14). The location of regurgitation may be important in PH. From an anatomical perspective, the function of the posterior mitral leaflet is more dependent to annular geometry because the posterior leaflet has a longer circumferential length compared to the anterior mitral leaflet, which is firmly attached to the fibrous trigon. One study showed that MR due to posterior leaflet prolapse was more vulnerable to abrupt increases in dynamic MR, exercise-induced PH (15) and poorer clinical outcomes compared to anterior leaflet prolapse (16).

Limitation of PH assessment with exercise echocardiography

As many patients with primary MR present PH only during exercise, evidence for exercise-induced PH in primary MR has long been awaited. However, resting SPAP still shows better prognostic power than peak-stress SPAP (6). Several issues should be considered for the assessment of PH with exercise echocardiography. First, accurate cutoff values to define exercise-induced PH are unknown. Data that would enable to the differentiation between normal versus abnormal pulmonary vascular response to exercise in primary MR remains insufficient (1). Magne *et al*. included 102 patients with primary MR and no or mild symptoms and showed that exercise PH, defined as peak-stress SPAP >60 mmHg, was associated with higher left atrial size, exercise-induced increased MR and long-term cardiac events during a mean 50±23 months after MV surgery (13). Despite this timely and elegant result, it was not enough to fill the gaps in the evidence because these results may be overemphasized by soft cardiac events including atrial fibrillations, which comprised 67% of the total events. Another limitation of exercise echocardiography is that the quantification of peak-stress SPAP is technically demanding compared with resting SPAP. As well as suboptimal alignment and strength of Doppler signal, the accuracy of echocardiography-derived peak-stress SPAP requires additional validation. For example, the correlation of echocardiographic SPAP with cardiac catheterization is weak in advanced emphysema (17). Errors in SPAP echocardiographic estimation may be larger depending on increasing blood flow volume and velocity during exercise.

Lastly, exercise-induced PH tends to occur at patients with high resting SPAP (6,13). Exercise-induced PH signifies the MR severity and pulmonary vascular remodelling, which could be expected by a resting SPAP around ≥35 mmHg. Additive information by peak stress SPAP is unclear.

Further questions

The results of Mentias *et al.* (7) raise several questions about the role of PH in primary MR. Firstly, is resting SPAP really enough? The study was performed retrospectively, and variables related to invasive cardiac catheterization, exercise stress test or LV strain analysis were not included. Although resting SPAP is a strong and reliable echocardiographic variable, whether it can substitute for the information of invasive or exercise-stress related examination is not clear. A second question surrounds the impact of the haemodynamic subset of exercise-induced PH in primary MR. Exercise-induced PH may develop with variable haemodynamics in primary MR. Some patients have combined pre-capillary PH with elevated pulmonary vascular resistance (12). Does increased pulmonary vascular resistance have adverse impact on long-term prognosis of patients with primary MR? Or, does MR severity matter? There are no data regarding the prognosis of different haemodynamic subsets. Lastly, should we prefer early surgery to prevent PH in primary MR? SPAP, whether at rest or during exercise, tends to be higher in cases with longer and more advanced MR (13). MV surgery is associated with improved long-term survival in primary MR (7). In patients with already developed pulmonary vascular remodelling, the degree of SPAP reduction could be minimal despite the optimal correction of valvular abnormality (18). Significant PH is associated with long-term mortality. Early surgery before the development of PH may improve short- and long-term outcomes. However, the evidence on whether early surgery for primary MR can prevent PH and reduce mortality is still lacking. In conclusion, recent studies have continuously validated the prognostic significance of PH in primary MR. The quantification of SPAP by echocardiography could stratify short- and long-term risks in patients with primary MR. As the risk begins to increase with even mild PH, the threshold for surgical timing before the development of pulmonary vascular remodelling should be considered in primary MR.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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