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EDITORIAL

Coronary microvascular reserve and outcome in aortic stenosis: Pathophysiological significance vs. clinical relevance

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This editorial refers to 'Comparison of exercise testing and cardiovascular magnetic resonance-measured myocardial perfusion reserve for predicting outcome in asymptomatic aortic stenosis: the PRognostic Importance of MIcrovascular Dysfunction in Aortic Stenosis (PRIMID AS) study', by A. Singh *et al.* doi:10.1093/eurheartj/ehx001.

Degenerative aortic stenosis (AS) is one of the most common valvular diseases in developed countries.[1] AS is a progressive disease for which the only effective treatment is surgical or transcatheter aortic valve replacement (AVR).[2,3] Patients with mild to moderate AS require no specific valve treatment, whereas AVR is indicated in patients with severe symptomatic AS. The main conundrum in the management of AS relates to the timing of AVR in almost half of the patients who have severe AS but do not report clinical symptoms at the time of diagnosis.[4] This uncertainty is mainly fed by the fact that no study has so far compared prospectively the outcomes in asymptomatic patients with severe AS undergoing watchful waiting and those undergoing AVR. Analysing all the previous studies reporting all-cause mortality in patients with asymptomatic AS who underwent AVR and those managed conservatively pointed to significant bias and data heterogeneity, preventing any valid conclusion.[5] Delaying AVR in severe AS until symptoms appear represents for most clinicians the fear that patients may present with irreversible myocardial damage, sudden cardiac death, or a rapidly progressive disease, especially in the absence of appropriate monitoring.[6] Hence, there is a crucial need to enable a prospective detection of patients with AS who will benefit from AVR before they become symptomatic. Based on the pathophysiological events occurring during valvular and myocardial remodelling in AS, several clinical, biological, and imaging parameters are currently being considered at different levels of evidence to help decision-making in asymptomatic severe AS.[7]

Coronary microvascular dysfunction is a major player both in the mechanism of angina and in the onset of the adverse myocardial remodelling in severe AS.[8] It can be detected as a myocardial perfusion defect in the absence of obstructive epicardial coronary artery disease, and quantified using various techniques including radionuclide imaging and cardiovascular magnetic resonance (CMR) through the myocardial perfusion reserve (MPR), the ratio of myocardial blood flow during maximal hyperhaemia at exercise and at rest.[9,10] The fact that clinical symptoms occur at the end of the ischaemic cascade, later after perfusion abnormalities could be detected, places a great expectation in the evaluation of MPR in AS.

In the current issue of the journal, Singh *et al.* investigated the potential role of comprehensive CMR relative to symptom-limited exercise testing (ETT) to predict the outcome in asymptomatic AS [PRognostic Importance of MIcrovascular Dysfunction in Aortic Stenosis (PRIMID AS) study].[11] Such an investigation is highly relevant, as the occurrence of typical symptoms during exercise testing is the sole robust class I indication for AVR in AS patients who claimed to be asymptomatic.[2,3] The way in which this observational study has been conducted is exemplary, as this prospective, multicentre investigation has placed special emphases on carefully mitigating some heterogeneity bias (i.e. exclusion of patients being referred for AVR prior to the onset of spontaneous symptoms), though the combined outcome remains a soft endpoint. The primary endpoint occurred in 47 of the 174 (27%) recruited patients over a median follow-up time of ~1 year. As expected, both low MPR and symptom-limited ETT were significantly associated with short-term occurrence of symptoms, but: (i) the value of both tests in predicting the outcome was moderate; (ii) MPR did not perform better than symptom-limited ETT; (iii) only symptom-limited ETT was associated with the outcome on the multivariable analysis, irrespective of the severity of AS; and (iv) the receiver operator characteristic (ROC) curves of both tests predicting the onset of symptoms were almost identical, showing moderate accuracy (areas under ROC curves ranging between 0.56 and 0.61), with low positive predictive values and high negative predictive values.

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This study confirms that reduced coronary flow reserve seems to be weakly associated with the development of symptoms in AS, despite being an independent predictor of exercise capacity, inversely associated with NYHA class in patients with severe AS undergoing AVR, and able to predict an ischaemic event (i.e. myocardial infarction) during non-cardiac surgery in AS.[12,13] Indeed, the onset of symptoms in the individual patient with AS also depends on the severity of the aortic obstruction, as well as on left ventricular (LV) function/remodelling, and the status of the peripheral circulation. When peripheral demands exceed the cardiac output, symptoms can occur (*Figure 1*). With exercise, cardiac output rises incrementally with workload. Increased cardiac output in severe AS is largely dependent on increased heart rate and the coronary flow reserve (ability of the coronary circulation to increase flow to match myocardial demand) that can be altered in the case of abnormal cardiac–coronary coupling, microvascular disease, or epicardial coronary artery stenosis.[10,14] Moreover, patients with AS (i) may be unable to augment coronary blood flow in response to increased myocardial workload, because vasodilation may already be near maximal; (ii) diastolic perfusion time is limited with increased heart rate; and (iii) there is a rapid increase in LV end-diastolic pressure, which further reduces the effective pressure gradient for perfusion.[14] All this creates an environment vulnerable to ischaemia that contributes to limited contractile function recruitment with subendocardial myocardial dysfunction during exercise, and, as such, provides a possible mechanism for exercise-induced symptoms (e.g. dyspnoea or angina) and intolerance. Beyond exhausted coronary flow reserve, the absence of contractile reserve during exercise can also reflect the presence of a more advanced disease stage, with extensive myocardial fibrosis and myocyte degeneration contributing to a mismatch between exercise afterload changes and contractility. A low flow state with no change or even a decrease in transaortic pressure gradients during exercise has been described in this latter condition.[4,7] So, all these complex interplays contribute to the limited accuracy of CMR MPR and exercise ECG changes to predict clinical deterioration in patients with asymptomatic AS, though both explore roughly the same phenomenon, i.e. coronary flow reserve and ischaemia. The higher number of females reaching the primary outcome in the study of Singh *et al.* also highlights the gender specificities regarding the LV remodelling process, smaller cardiac volumes and more concentric LV geometry, different coronary flow reserve with higher resting and hyperaemic myocardial blood flow than men, and distinctive responses to ischaemia and exercise (a more inconclusive test).[4,11,14] In practice, the present data pointed out that no single test enables accurate stratification of asymptomatic patients with severe AS, which calls for multiparametric strategies exploring distinct pathways in the future. However, the use of MPR may still be considered as an alternative to exercise testing, because of several advantages over ETT, including notably a lower rate of inconclusive examinations, and an objective quantification of the microvascular dysfunction as well as LV function and remodelling.

Cardiac magnetic resonance also has the ability to characterize the pattern and volume of myocardial fibrosis (focal vs. diffuse; subendocardial vs. midwall).[4] Recent studies have shown that the presence of myocardial fibrosis in the midwall layer is more specific to pressure overload cardiomyopathies, such as in AS, rather than to ischaemic heart disease.[4,15] Whether the localization and quantification of myocardial fibrosis by CMR may be potentially useful to optimize risk stratification and timing of AVR in asymptomatic patients with severe AS is unknown. In their study, Singh *et al.* have also specifically addressed, for the first time, the question regarding the use of late-gadolinium enhancement (the degree of focal fibrosis corresponding to replacement fibrosis) and extracellular volume (diffuse fibrosis corresponding to reactive interstitial fibrosis) measurements, both obtainable in the same examination session as MPR.[11] Although fibrosis is thought to play an important role in the pathophysiology of AS, the current study showed that both measurements were not predictive of the outcome in asymptomatic AS. Only a very small difference in extracellular volume (1%) between those with and without an outcome was observed. Actually CMR features of myocardial fibrosis have been extensively evaluated mainly in symptomatic patients with and without heart failure,[15,16] and the findings of the present study are nothing less than confirmation that extensive myocardial fibrosis occurs later in the course of the disease. However, since the number of clinical events was relatively low and a combined soft clinical endpoint was used, these data need to be confirmed in a larger cohort of patients with severe AS.

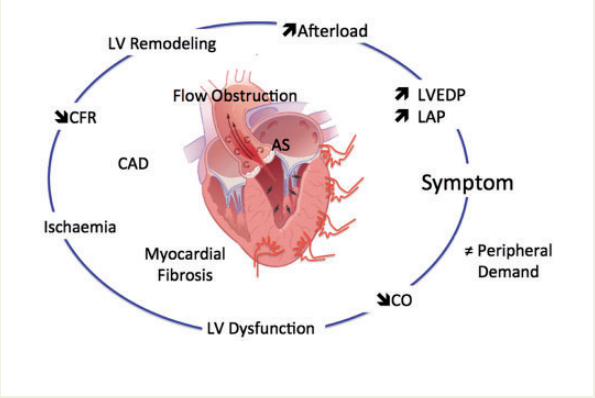

Figure 1 Schematic representation of the multifactorial factors contributing to the development of symptoms in patients with aortic stenosis (AS). CAD, coronary artery disease; CFR, coronary flow reserve; CO, cardiac output; LAP, left atrial pressure; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure.

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