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Clinical impact of myocardial fibrosis in severe aortic stenosis

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The pressure overload due to the progressive narrowing of the valve area determines the development of the left ventricular hypertrophy which characterizes aortic stenosis (AS). The onset of myocardial fibrosis marks the inexorable decline of an initially compensatory response towards heart failure. However, myocardial fibrosis does not yet represent a key element in the prognostic and therapeutic framework of AS. In this context, cardiac magnetic resonance imaging plays a major role by highlighting both the focal irreversible fibrotic replacement, using the late gadolinium enhancement (LGE) technique, and the earlier diffuse reversible interstitial fibrosis, using the T1 mapping techniques. For this reason, the presence of myocardial fibrosis would be useful to identify a subgroup of patients at greater risk of events among the subjects with severe AS. Actually, more and more evidences seem to identify the presence of LGE as a powerful prognostic factor to be used to optimize the timing of prosthetic valve replacement. Randomized clinical trials, such as the EVoLVeD trial currently underway, will be needed to better define the importance of myocardial fibrosis assessment in the management of patients with AS.

Introduction

Aortic stenosis (AS) is a disease of both aortic valve and myocardium, in which the hypertrophy is the natural response to the pressure overload caused by the progressive aortic valve narrowing. Myocardial fibrosis is an expression of the hypertrophic remodelling and marks the negative evolution of the initially compensatory response to the aortic outflow obstruction. Cardiac magnetic resonance (CMR) is the main tool for the study of myocardial fibrosis ensuring, in a non-invasive way, the tissue characterization of the heart muscle, the functional evaluation of the heart pump, and the quantification of replacement fibrosis affecting the entire myocardium through the late gadolinium enhancement (LGE) technique.

In Europe, CMR is used for the evaluation of myocardial fibrosis in AS in a limited proportion of cases, estimated at 21% according to a recent European survey.[1]

Depending on the case series, the prevalence of LGE in moderate–severe AS varies between 30% and 60% of the entire cohort.[2–4] The clinical impact of myocardial fibrosis in AS is discussed below.

The pathophysiology behind fibrosis

It is now well established that left ventricular hypertrophy is the key response to the increased left ventricular systolic pressure in AS.[5] Recent studies, however, have questioned the beneficial role of left ventricular hypertrophy in AS, suggesting instead that the increase in myocardial mass should be interpreted as a predictor of left ventricular dysfunction.[6] This is due to the fact that the myocardial degeneration and fibrosis can favour the stiffness of the heart

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muscle and the transition from a compensatory response to heart failure.[4]

However, myocardial fibrosis in AS should not be considered as a static entity, but part of a process of response and adaptation to an unfavourable haemodynamic condition. In the early stages, fibrosis is reactive, interstitial and involves the myocardium diffusely and it is reversible after aortic valve replacement (AVR).[7] Subsequently, with the persistence of pressure overload and the consequent wall stress, the fibrosis becomes substitutive, irreversible and with a focal distribution.[8]

Cardiac magnetic resonance

In recent decades, CMR has assumed a central role in the characterization of soft tissues and in the identification of cardiac fibrosis, both diffuse and focal. In this context, the LGE technique permits to magnify the areas of focal replacement since these areas, discarding the gadolinium-based contrast medium slowly, have a reduced T1 compared to healthy myocardium. Using dedicated software, the amount of myocardium replaced with fibrosis can be quantify as percentage of the total cardiac mass. Good correlation between the quantification of LGE on CMR and the histological determination of fibrosis has been shown in patients with AS.[2]

Replacement fibrosis can assume a subendocardial or transmural (ischaemic) pattern, or an intra-myocardial (non-ischaemic) pattern.[9] Given the high prevalence of coronary heart disease in patient with AS, this aspect is not of secondary importance. In fact, the difficulty in distinguishing between the focal myocardial fibrosis due to epicardial coronary disease, and the myocardial fibrosis due to the imbalance between oxygen demand and supply proper to the hypertrophic left ventricle, raises a problem of differential diagnosis. Albeit with a small sample of patients, in an elegant study by Dweck *et al.*,[3] the presence of LGE with ischaemic pattern was associated with a more severe coronary artery disease and a worse left ventricular ejection fraction, while the non-ischaemic pattern was associated with a greater hypertrophy and a history of arterial hypertension. Regardless of the type of pattern, the presence of LGE in subjects with severe AS describes a patient at increased risk for adverse events.[2–4,10] Diffuse interstitial fibrosis, on the other hand, is not intercepted by the LGE sequences since the contrast medium is equally distributed throughout the myocardium. The recovery times of longitudinal magnetization (T1 mapping) aim to overcome this aspect, as the native T1 values reflect the state of the myocardium as a whole. Theoretically, since the presence of fibrosis raises the native T1 value, the T1 mapping technique would allow to discriminate between a healthy myocardium and a myocardium with diffuse fibrosis not visible in the LGE sequences. On the other hand, the use of the contrast medium and the acquisition of pre and post administration T1 maps, would allow to specifically explore the extracellular volume (ECV) and therefore estimate the amount of interstitial fibrosis. However, the dependence of T1 mapping on numerous variables related to the patient, the physical environment, the hardware for the acquisition and the software for the post-processing of the images, makes the method reproducible only within the same structure after validation of cut-off values derived from the same laboratory.[11]

The prognostic role of the late gadolinium enhancement

As demonstrated in other pathologies, the presence of LGE also proved to be a powerful predictor of mortality and adverse cardiovascular events in AS. Weidemann *et al.*[12] were the first to explore the role of LGE in patients with symptomatic severe AS: of 58 AVR candidates, 15 had mild LGE and 21 severe. The extent of fibrosis correlated with the functional class and the longitudinal systemic function indices but not with the ejection fraction or the transvalvular gradient. Furthermore, the presence and greater extension of the LGE was associated with a lesser functional recovery after AVR.

In a study of Dweck *et al.*,[3] of 143 enrolled patients, 49 (34%) did not have LGE, while the remaining 94 (66%) showed areas of hyper-intensity at the LGE sequences, of which 40 (28%) with ischaemic pattern and 54 (38%) with non-ischaemic pattern. The presence of LGE was associated with a six- and eight-fold increase in mortality, respectively. Multivariate Cox analysis confirmed the left ventricular ejection fraction [hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.94–0.99; $P = 0.009$] and the non-ischaemic pattern LGE (HR 5.35; 95% CI 1.16–24.56; $P = 0.0034$) independent predictors of mortality from all causes.

The prognostic role of the LGE was then validated in a study of Barone-Rochette *et al.*[4] that, focusing on the perioperative risk in 154 patients with severe AS with no history of myocardial infarction undergoing surgical AVR, identified the LGE as a robust predictor of postoperative mortality (HR 2.1; 95% CI 1.1–6.9; $P = 0.025$), independently of the presence of significant coronary artery disease at baseline. Similarly, of 40 patients with AS undergoing percutaneous AVR, an increased cardiovascular mortality was observed among those presenting with LGE on CMR. Comparing the two populations, LGE was present in 29% of patients undergoing surgical AVR and in 50% of patients undergoing transcatheter AVR, reflecting the more advanced New York Heart Association functional class population (27% vs. 57%), higher incidence of severe coronary heart disease treated with angioplasty (3% vs. 25%), and more impaired ejection fraction (median value 60% vs. 50%).

Subsequently, data from the 'BSCMR Valve Consortium' showed that, of 674 patients with severe AS and preserved left ventricular systolic function listed for AVR, the presence of myocardial fibrosis was found in 51% of patients at baseline (18% with ischaemic pattern, 33% with non-ischaemic pattern). All patients underwent AVR (399 surgical and 275 transcatheter). In the multivariate analysis, factors independently associated with all-cause mortality were age, the Society of Thoracic Surgeons score and the presence of LGE at CMR (HR 2.39; 95% CI 1.40–4.05; $P = 0.001$). Each 1% increase in the extent of left ventricular myocardial fibrosis was associated with a risk of all-

cause mortality greater than 11% (HR 1.11; 95% CI 1.05–1.17; $P < 0.001$) and a risk of cardiovascular mortality greater than 8% (HR 1.08; 95% CI 1.01–1.17; $P < 0.001$).[13]

A systematic review of six studies, by Papanastasiou *et al.*,[14] evaluated the prognostic value of LGE in patients with AS, which is shown to be associated with a more than two-fold increase in the risk of mortality from all causes, even after adjustment for baseline characteristics [OR 2.56 (95% CI 1.83–3.57); HR 2.50 (95% CI 1.64–3.83)].

Ultimately, LGE is proposed as a new imaging biomarker for risk stratification in AS patients. The presence/absence of fibrosis could be a useful tool in defining the timing of AVR and in choosing the most appropriate method between surgery and percutaneous replacement.[15] However, myocardial fibrosis is not currently part of the routine evaluation in AS patients and the clinical decision regarding valve replacement is mainly based on the patient's clinical data, such as the development of typical symptoms, the extent of the transvalvular gradient, the reduction of left ventricular ejection fraction <50%, stress test abnormalities, and increased natriuretic peptide levels.[16,17]

T1 native and extracellular volume

Recently, numerous studies have investigated the role of T1 mapping in the prognostic stratification of patients with moderate–severe AS, demonstrating its predictive value in terms of increased adverse events, regardless of the therapeutic programme, and in terms of reverse remodelling and prognosis after valve replacement.[18,19]

Mostly, Everett *et al.*[20] suggested the possibility of conducting a multicentre study based on the use of the T1 mapping technique. The authors demonstrated a good overlap between the measurements carried out in different centres, using scanners of different brands, operating at variable magnetic fields (1.5 T and 3 T) and with diversified acquisition protocols, thus overcoming the big problem related to the lack of reproducibility of the value of native T1 and ECV between different centres. In truth, this data were confirmed only for the ECV expressed as a percentage, while the native T1 values proved not to be reproducible between different centres, as expected. Furthermore, they have documented that mortality from all causes in patients with AS waiting for AVR progressively increases as the ECV increases, with a 10% increase in mortality for every 1% increase in ECV. It is thus stated that interstitial fibrosis quantified with the T1 mapping technique at CMR constitutes an independent predictor of mortality, which overcame age, sex, reduced ejection fraction of the left ventricle (<50%), and LGE at the multivariate Cox analysis. If the ECV, intercepting early diffuse interstitial fibrosis, has a better predictive role of mortality than LGE, which identifies the replacement fibrosis characteristic of the more advanced stages, still an open question. Moreover, considering also the wide variability of the T1 mapping and ECV values determined by the aforementioned factors, as well as the lack of expertise relating to the not widespread method, we can understand how this mapping technique is as promising as immature to play a decisive role in the clinical management of the patient.

Conclusions

The presence of myocardial fibrosis identifies a subgroup of patients at greater risk of events among subjects with severe AS. The data currently available seem to recognize myocardial fibrosis as an additional factor in the prognostic stratification of patients with severe AS, speculating its possible key role in the selection of candidates for AVR. Some responses will derive from the ongoing Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS (EVoLVeD) trial (NCT03094143) which aims to explore the role of myocardial fibrosis in the indication of AVR compared to the traditional 'watchful and waiting'.[21]

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