EDITORIAL COMMENT

Predicting outcomes from myocardial fibrosis in aortic stenosis. A view from histopathology

A fibrose miocárdica na predição de prognóstico da estenose aórtica. Uma perspetiva da histopatologia

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Available online 10 December 2021

Aortic stenosis (AS) is the most frequent valvular heart disease in the western world and a health social burden due to its increasing prevalence with aging and its inexorable progression both in severity and myocardial consequences.

Severe AS is currently treated with surgical or percutaneous valve replacement, leading to significant improvement in the prognosis of patients with this valvular heart disease. However, long-term prognosis depends also on additional variables that impact on quality of life and survival.

Left ventricular (LV) remodeling has been recognized as a key mechanism underlying prognosis, alongside ultimate maladaptive hypertrophy, progressive myocardial fibrosis and myocyte death, as shown from histopathology. Hypertrophic response in aortic stenosis cannot be accurately predicted from the degree of valve narrowing alone. Importantly, myocardial fibrosis has been shown by pathologists as a key process that drives the transition from hypertrophy to heart failure, although progression patterns and evolved mechanisms still require clarification.

In fact, in spite of successful aortic valve replacement, myocardial fibrosis diagnosed by histopathology at the time of aortic valve repair (AVR) has been found to be inversely related to post-surgical LV function and wall thickness, and directly related to late cardiac mortality.²,³

Myocardial fibrosis has two different patterns and stepped progression has been described in AS with myocardial interstitial fibrosis as the first process to occur, followed by replacement fibrosis in more advanced disease, representing the ultimate irreversible event at the time of AVR and a more significant impact on long-term outcome.²,⁴,⁵

Among the mechanisms underlying fibrosis development in association with hypertrophy in AS, the evolving reduced capillary density and myocardial ischemia, followed by apoptosis and necrosis, are proposed as main factors.⁶ However, fibrosis has also been shown to be regulated by non-hemodynamic factors such as angiotensin II, metalloproteinases as well as other neurohormones, that are likely major contributors regardless of the level of hypertrophy and stenosis severity.⁷ In fact, the remodeling responses to AS overload seem to vary among individuals not only regarding the degree of hypertrophy but also the mechanisms leading to the amount of fibrosis development.

It is therefore crucial to identify accurate diagnostic methods that enable early detection of adverse remodeling as preceding the development of the whole process that leads ultimately to irreversible fibrosis and adverse prognosis, in spite of successful aortic valve replacement.

In the present paper, Gavina et al.⁸ assessed the amount of myocardial fibrosis determined by histopathology in patients with severe AS and normal or mildly depressed ejection fraction (EF) (>40%) obtained from endomyocardial biopsies at the time of surgical aortic valve replacement.

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A quantitative estimate of myocardial fibrosis showed that higher levels of fibrosis were associated with all-cause death or non-fatal cardiovascular hospitalizations, independent of EF, age and myocardial mass. They found that a cut-off value of 15% for collagen volume fraction, expressing a percentage of fibrosis from myocardial volume, was a predictor of late clinical events.

Previous histopathological work in AS patients also found a relationship, but the population included patients with both a large range of ejection fraction values and myocardial fibrosis, in relation to different phases of evolution at the time of AVR, thus with a proportion of patients with more advanced myocardial disease, in contrast to the current study.

The present study is important since it concerns a population with normal or mildly depressed EF. This would suggest that even at an early phase of LV remodeling, where the extent of fibrosis should be less prominent and a parallel benign long-term outcome should be expected, and in spite of the low mean percentage of fibrosis found, the amount was independently related to prognosis. This might open doors to acting earlier on aortic valve intervention. Both the limited population of the present study and the use of EF as a surrogate marker of LV function, albeit the most widely used left ventricular functional index, preclude definite directions on the diagnosis and management of AS. However, this study is important and confirms the need for additional larger studies to corroborate the results.

In recent years, cardiac magnetic resonance (CMR) has opened up new possibilities for predicting outcomes in AS based on fibrosis, as it detects and quantifies both interstitial and focal fibrosis, using respectively T1 mapping and late gadolinium enhancement (LGE). The link between histopathology and non-invasive CMR myocardial changes seems now to be strong enough to enable a non-invasive assessment and supports a translational approach for following these patients. Azevedo et al.\(^1\) showed a good correlation between the amount of fibrosis assessed using contrast enhanced CMR and histopathology. In a large study of 650 patients, Musa et al.\(^2\) described LGE as the most powerful predictor of late mortality. Chin et al.\(^3\) recently showed that both focal and interstitial fibrosis were unrelated to AS severity while they were associated with worse outcomes, particularly LGE. Moreover, interstitial fibrosis predicted the development of late focal fibrosis, and was proposed as an intermediate and possibly reversible phase of fibrosis.

These papers together show that non-invasive study using CMR has the potential to identify fibrosis noninvasively and that it is useful for following these patients and assessing outcomes. However, LGE has been found only in late phases of evolution and the role of T1 mapping is not yet clearly defined in all subsets of AS patients, since values overlap in AS severity and changes are subject to other influences that may act as confounders (such as concomitant hypertension).

In conclusion, we might say that fibrosis is a key point in myocardial remodeling and has an impact on LV diastolic function and late systolic function. In AS, fibrosis is a hallmark of pressure overload before AVR. However, myocardial fibrosis does not relate directly to the severity of stenosis, but is also modeled by neurohormonal and genetic influences, thus translating individual responses into systolic stress. Fibrosis leads to more fibrosis, less capillary density, ischemia and ultimately interstitial fibrosis can evolve to irreversible replacement fibrosis.

Although not clearly established, it could be key to detect fibrosis early in the evolution of AS even in low-risk patients with normal or mildly reduced LV ejection fraction, in order to positively influence the late prognosis of these patients. The present paper, highlights that myocardial fibrosis is present well before significant LV dysfunction, hypothesizing that early aortic valve intervention and acting on the neurohormonal axis could benefit long-term prognosis before myocardial fibrosis is established and irreversible.

Future work should be undertaken to confirm these hypotheses, identifying and refining the best time for valve intervention. However, the authors should be congratulated on the present study, which suggests that even in low-risk patients without significant EF depression, fibrosis is present and has an impact on prognosis. This is very likely a path toward improving prognosis in AS.

### Conflicts of interest

The author has no conflicts of interest to declare.

### References