Assessment of diffuse myocardial fibrosis in aortic valve stenosis: let’s get personal

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Owing to continuous advances in both cardiovascular surgery and interventions, there is nowadays a whole range of therapeutic options that can be offered to patients with valvular heart disease. In the case of aortic valve stenosis, patients without major co-morbidities can undergo surgical aortic valve replacement (AVR) at a very low surgery-related risk for major adverse events. On the other end of the spectrum, patients who are judged to be too sick to undergo surgery might benefit from transcatheter aortic valve implantation.

While the reduction in procedure-related complications is an important advance over the state from a few decades ago, the decision-making process leading to valve replacement is still based on the same mechanistic concepts that were used at the time when valve replacement surgery first became available. Specifically, parameters such as pressure gradients, regurgitant fractions, and ventricular volumes are taken into account in order to estimate the impact of valvular dysfunction on the affected ventricle. Although these parameters have been shown to identify groups of patients who do better with therapy than without, it seems questionable if they are well suited to determine the best time point for that decision during the course of disease in an individual patient.

An abnormal increase in the interstitial collagen content, i.e. the development of diffuse myocardial fibrosis, has been shown to be an essential step in the transition from cardiac adaption to failure in chronic valvular disease. Cardiac magnetic resonance (CMR) enables the estimation of the extracellular volume (ECV) fraction by means of the quantification of the myocardial gadolinium content using T1 mapping. Flett et al. recently demonstrated that ECV (equivalent to myocardial volume of distribution, Vd,m), as assessed in steady state of the contrast agent’s concentrations in the myocardium and the blood pool achieved by a bolus—infusion protocol (equilibrium contrast CMR), directly correlates with the collagen content as assessed by myocardial biopsy. In this issue of European Heart Journal – Cardiovascular Imaging, the same group presents the results of a prospective study on patients with severe aortic valve stenosis scheduled for AVR. Patients underwent equilibrium contrast CMR before and 6 months after AVR, along with a repeated clinical assessment, echocardiography, 6-minute walk test (6-MWT), and the measurement of brain natriuretic peptide. The authors found that the extent of diffuse myocardial fibrosis inversely correlated with the performance at the 6-MWT, and that it also correlated with the change in the post-operative 6-MWT performance on univariate but not multivariate analysis. Moreover, four out of the five deaths occurring during the 6-month follow-up period occurred in patients of the highest tertile of diffuse myocardial fibrosis.

Through the assessment of ECV, diffuse myocardial fibrosis finally has become directly assessable in a non-invasive manner for both clinical and preclinical applications. With their present study, Flett et al. for the first time provide evidence of the prognostic value of ECV in patients with aortic valve stenosis, marking an important milestone on the road towards clinical application of this technique. The findings support the hope that ECV might be a direct marker of the impact of valvular disease on the myocardium. Thus, ECV could be a better predictor of the long-term benefit from AVR than conventional non-invasive parameters, and allow for a personalized decision on the timing of therapeutic procedures.

From a methodological point of view, the optimal approach for the assessment of ECV is currently under investigation by several groups involved in CMR research. Points under discussion include the optimal choice for the T1 mapping pulse sequence, the best injection protocol for the contrast agent (bolus vs. bolus—infusion protocols), and advanced post-processing techniques (e.g. automated motion correction). To allow for better comparison of different approaches and to facilitate their use for physicians and scientists new to the field, an international working group on cardiac T1 mapping has been formed. This group is working on a framework for systematic application of and research on cardiac T1 mapping and assessment of ECV. With optimized methodology, further studies should investigate the prognostic value of ECV in patients with moderate disease, and multi-centre trials should be initiated in order to define the clinical role for ECV measurements. This may enable physicians in the future to give more individual answers to the individual situations of their patients.
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**References**


**IMAGE FOCUS**

**Incremental value of three-dimensional strain imaging in Danon disease**

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A 43-year-old woman with a familial history of Danon disease and early sudden death was clinically followed because of carrier of LAMP-2 mutation. She was symptomatic for palpitations. Clinical evaluation and electrocardiogram were normal (Panel A), while Holter monitoring revealed non-sustained ventricular tachycardia (VT; Panel B). Conventional two- and three-dimensional echocardiograms were unremarkable (see Supplementary data online, Movie S1); however, three-dimensional speckle-tracking imaging (3D-STI) revealed an impairment of the longitudinal strain of the basal segment of the inferior wall (blue area of the bull’s eye in Panel C). Contrast-enhanced cardiac magnetic resonance showed late gadolinium enhancement in the same area, indicating the presence of myocardial fibrosis (Panel D). Based on these findings and clinical data, the patient subsequently underwent implantable cardioverter-defibrillator (ICD) implantation and, shortly after, she received an appropriate ICD intervention for sustained VT.

Danon disease is a rare X-linked systemic disorder due to lysosome dysfunction affecting mainly young males; it is characterized by hypertrophic cardiomyopathy, skeletal myopathy, and mental retardation, leading to rapid clinical deterioration and death. LAMP-2 mutation results in profound myocardial structural abnormalities with extensive scarring replacement and autophagic and vacuolated myocytes; these may lead to life-threatening arrhythmias. Different phenotype expressions have been described in females ranging from asymptomatic carriers to hypertrophic or dilated cardiomyopathy with severe arrhythmogenic trait.

This case illustrates the potential role of new echocardiographic techniques for myocardial strain evaluation in risk stratification of female LAMP-2 mutation carriers. Three-dimensional STI may permit early recognition of cardiac involvement, through the detection of concealed myocardial abnormalities related to the presence of fibrosis, and guide ICD implantation.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.