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Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis

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ABSTRACT

BACKGROUND Left ventricular (LV) hypertrophy, a key process in human cardiac disease, results from cellular (hypertrophy) and extracellular matrix expansion (interstitial fibrosis).

OBJECTIVES This study sought to investigate whether human myocardial interstitial fibrosis in aortic stenosis (AS) is plastic and can regress.

METHODS Patients with symptomatic, severe AS ($n = 181$; aortic valve area index 0.4 ± 0.1 cm^2/m^2) were assessed pre-aortic valve replacement (AVR) by echocardiography (AS severity, diastology), cardiovascular magnetic resonance (CMR) (for volumes, function, and focal or diffuse fibrosis), biomarkers (N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T), and the 6-min walk test. CMR was used to measure the extracellular volume fraction (ECV), thereby deriving matrix volume (LV mass × ECV) and cell volume (LV mass × [1 − ECV]). Biopsy excluded occult bystander disease. Assessment was repeated at 1 year post-AVR.

RESULTS At 1 year post-AVR in 116 pacemaker-free survivors (age 70 ± 10 years; 54% male), mean valve gradient had improved (48 ± 16 mm Hg to 12 ± 6 mm Hg; $p < 0.001$), and indexed LV mass had regressed by 19% (88 ± 26 g/m^2 to 71 ± 19 g/m^2; $p < 0.001$). Focal fibrosis by CMR late gadolinium enhancement did not change, but ECV increased (28.2 ± 2.9% to 29.9 ± 4.0%; $p < 0.001$): this was the result of a 16% reduction in matrix volume (25 ± 9 ml/m^2 to 21 ± 7 ml/m^2; $p < 0.001$) but a proportionally greater 22% reduction in cell volume (64 ± 18 ml/m^2 to 50 ± 13 ml/m^2; $p < 0.001$). These changes were accompanied by improvement in diastolic function, N-terminal pro-B-type natriuretic peptide, 6-min walk test results, and New York Heart Association functional class.

CONCLUSIONS Post-AVR, focal fibrosis does not resolve, but diffuse fibrosis and myocardial cellular hypertrophy regress. Regression is accompanied by structural and functional improvements suggesting that human diffuse fibrosis is plastic, measurable by CMR and a potential therapeutic target. (Regression of Myocardial Fibrosis After Aortic Valve Replacement; NCT02174471) (J Am Coll Cardiol 2018;71:860–71) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Aortic stenosis (AS) is the most common valve disease and a prototype model for afterload-induced heart failure (1,2). Progressive aortic valve stenosis affects the left ventricle, which adapts to reduce wall stress and maintains cardiac output. Macroscopic adaptations are detected as left ventricular (LV) hypertrophy (LVH), whereas microscopic changes are characterized by cardiomyocyte hypertrophy and extracellular matrix expansion, caused by both focal replacement fibrosis (scar) and reactive, interstitial diffuse myocardial fibrosis (3–8).

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Following aortic valve replacement (AVR, surgical or transcatheter), LVH regresses by 20% to 30% by 1 year (9–11). Whether this regression is cellular or interstitial has until recently been difficult to differentiate because it requires paired biopsies for histological examination. Cardiac magnetic resonance (CMR) is established as a tool for quantification of focal fibrosis by late gadolinium enhancement (LGE), but with T_1 mapping CMR can now also measure diffuse fibrosis by quantifying the extracellular volume fraction (ECV). CMR with T_1 mapping differentiates between cellular (myocytes, fibroblast, endothelial, red blood cells) and extracellular (extracellular matrix, blood plasma) compartments (**Central Illustration**) (12–14), and it offers the opportunity to track dynamic changes in the cell and matrix compartments. In AS, outcome is predicted not only by the extent of LVH at baseline or its regression post-AVR (10,15–17), but also by focal fibrosis (using LGE) (3–5) and diffuse fibrosis (using ECV) (18,19). Histological studies show that myocardial fibrosis accompanies cellular hypertrophy (20), and limited invasive studies suggest that both may regress after AVR (21).

We aimed to demonstrate that human myocardial fibrosis is plastic and can regress after AVR and that this regression can be measured noninvasively.

METHODS

This prospective observational cohort study was conducted in patients with severe, symptomatic AS who underwent AVR between January 2012 and January 2015 in a single tertiary referral cardiac center, University College London Hospital NHS Trust, London, United Kingdom. The study was approved by the ethical committee of the U.K. National Research Ethics Service (07/H0715/101) and was registered with ClinicalTrials.gov (Regression of Myocardial Fibrosis After Aortic Valve Replacement; NCT02174471). The study conformed to the principles of the Helsinki Declaration, and all subjects gave written informed consent. Patients were recruited before preoperative evaluation. Pre-AVR and post-AVR, the comprehensive assessment included clinical history, blood pressure, 6-min walk test (6MWT) (22), blood sampling (for high-sensitivity troponin T [hsTnT] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]), electrocardiography, transthoracic echocardiography, and CMR using the same equipment. Inclusion criteria were adult patients with severe AS (2 or more of: aortic valve area <1 cm^2, peak pressure gradient >64 mm Hg, mean pressure gradient >40 mm Hg, aortic valve velocity ratio <0.25) who were undergoing AVR with or without coronary artery bypass grafting. Exclusion criteria were pregnancy or breastfeeding, estimated glomerular filtration rate <30 ml/min/1.73 m^2, CMR-incompatible implanted devices, inability to complete the protocol, previous valve surgery, or greater then moderate valve disease other than AS. Overall, 48% of patients undergoing surgical AVR for severe AS at our institution were recruited (**Figure 1**).

ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

AS = aortic stenosis

AVR = aortic valve replacement

CMR = cardiovascular magnetic resonance

ECV = extracellular volume fraction

hsTnT = high-sensitivity troponin T

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

LVM = left ventricular mass

LVMI = left ventricular mass index

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

MULTIMODALITY CARDIAC IMAGING. Echocardiography was used to assess diastolic parameters and valve area or velocities (with CMR for regurgitant volumes if needed). CMR cine imaging was used to assess LV structure and systolic function. CMR T_1 mapping and ECV were undertaken for myocardial tissue characterization. All analysis was performed by operators blinded to clinical parameters.

Echocardiography. Clinical transthoracic echocardiography was performed using a GE Vivid E9 system (GE Healthcare, Waukesha, Wisconsin) with a 4-MHz transducer, following the guidelines of the American Society of Echocardiography and the European Society of Echocardiography (23).

Cardiovascular magnetic resonance. CMR was performed at 1.5-T (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany), by using a standard clinical scan protocol with late gadolinium enhancement (LGE) imaging and T_1 mapping (by MOdified Look-Locker Inversion recovery [MOLLI]) (24) before and after a bolus of gadolinium contrast (0.1 mmol/kg of gadoterate meglumine [gadolinium-DOTA, marketed as Dotarem, Guerbet S.A., Paris, France]). Post-contrast imaging was performed at 10 min (LGE) and 15 min (T_1 mapping).

Imaging analysis. CMR image analysis was performed using CVI42 software (version 5.1.2[303],