JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2016

ISSN 1936-878X
http://dx.doi.org/10.1016/j.jcmg.2016.10.007

Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis

Calvin W.L. Chin, MD,[a,b] Russell J. Everett, MD,[a] Jacek Kwiecinski, MD,[a,c] Alex T. Vesey, MD, PhD,[a] Emily Yeung,[a] Gavin Esson,[a] William Jenkins, MD,[a] Maria Koo,[a] Saeed Mirsadraee, MD,[a] Audrey C. White,[a] Alan G. Japp, MD, PhD,[a] Sanjay K. Prasad, MD,[d] Scott Semple, PhD,[e] David E. Newby, MD, PhD,[a] Marc R. Dweck, MD, PhD[a]

ABSTRACT

OBJECTIVES Cardiac magnetic resonance (CMR) was used to investigate the extracellular compartment and myocardial fibrosis in patients with aortic stenosis, as well as their association with other measures of left ventricular decompensation and mortality.

BACKGROUND Progressive myocardial fibrosis drives the transition from hypertrophy to heart failure in aortic stenosis. Diffuse fibrosis is associated with extracellular volume expansion that is detectable by T1 mapping, whereas late gadolinium enhancement (LGE) detects replacement fibrosis.

METHODS In a prospective observational cohort study, 203 subjects (166 with aortic stenosis [69 years; 69% male]; 37 healthy volunteers [68 years; 65% male]) underwent comprehensive phenotypic characterization with clinical imaging and biomarker evaluation. On CMR, we quantified the total extracellular volume of the myocardium indexed to body surface area (iECV). The iECV upper limit of normal from the control group (22.5 ml/m^2) was used to define extracellular compartment expansion. Areas of replacement mid-wall LGE were also identified. All-cause mortality was determined during 2.9 $\pm$ 0.8 years of follow up.

RESULTS iECV demonstrated a good correlation with diffuse histological fibrosis on myocardial biopsies ($r = 0.87$; $p < 0.001$; $n = 11$) and was increased in patients with aortic stenosis (23.6 $\pm$ 7.2 ml/m^2 vs. 16.1 $\pm$ 3.2 ml/m^2 in control subjects; $p < 0.001$). iECV was used together with LGE to categorize patients with normal myocardium (iECV <22.5 ml/m^2; 51% of patients), extracellular expansion (iECV ≥22.5 ml/m^2; 22%), and replacement fibrosis (presence of mid-wall LGE, 27%). There was evidence of increasing hypertrophy, myocardial injury, diastolic dysfunction, and longitudinal systolic dysfunction consistent with progressive left ventricular decompensation (all $p < 0.05$) across these groups. Moreover, this categorization was of prognostic value with stepwise increases in unadjusted all-cause mortality (8 deaths/1,000 patient-years vs. 36 deaths/1,000 patient-years vs. 71 deaths/1,000 patient-years, respectively; $p = 0.009$).

CONCLUSIONS CMR detects ventricular decompensation in aortic stenosis through the identification of myocardial extracellular expansion and replacement fibrosis. This holds major promise in tracking myocardial health in valve disease and for optimizing the timing of valve replacement. (The Role of Myocardial Fibrosis in Patients With Aortic Stenosis; NCT01755936) (J Am Coll Cardiol Img 2016;■:■–■) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]BHF/Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom; [b]Department of Cardiovascular Science, National Heart Center, Singapore; [c]First Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland; [d]Royal Brompton Hospital, London, United Kingdom; and the [e]Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom. Dr. Chin was supported by the National Research Foundation, Ministry of Health, Singapore. Drs. Newby, Dweck, and Everett were supported by the British Heart Foundation (CH/09/002, FS/14/78/31020, and CH/09/002/26360, respectively). Dr. Dweck was also supported by the Sir Jules Thorn Biomedical Research Award 2015 (15/JTA). Dr. Newby was also supported by a Wellcome Trust Senior Investigator Award (WT103782AIA). Dr. Semple has been a consultant for GlaxoSmithKline. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Chin and Everett contributed equally to this work.

Manuscript received June 21, 2016; revised manuscript received October 4, 2016, accepted October 5, 2016.

ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

BNP = brain natriuretic peptide

CMR = cardiac magnetic resonance

cTnI = cardiac troponin I

ECV = extracellular volume

ECG = electrocardiogram

iECV = indexed extracellular volume

IQR = interquartile range

LGE = late gadolinium enhancement

LV = left ventricular

LVH = left ventricular hypertrophy

Calcific aortic stenosis is the most common valvular heart condition in the western world and a major public health burden (1). In recent years, the role of left ventricular (LV) remodeling in disease progression, symptom development, and adverse cardiovascular events in aortic stenosis has been increasingly appreciated (2). In the initial phases, the increased afterload imposed by aortic valve narrowing induces adaptive left ventricular hypertrophy (LVH) that acts to maintain wall stress and cardiac output. Ultimately, this process decompensates, and patients transition from hypertrophy to heart failure and the development of symptoms and adverse cardiovascular events (2,3). This transition often correlates poorly with the severity of aortic valve narrowing and is predominantly driven by myocardial fibrosis and myocyte cell death (4), which is perhaps a consequence of supply-demand mismatch and myocardial ischemia in the hypertrophied myocardium (2). Therefore, there is considerable interest in developing novel biomarkers to detect the early signs of LV decompensation.

Cardiac magnetic resonance imaging (CMR) provides the noninvasive gold standard method for measuring LV wall thickness, mass, volumes, and ejection fraction. Moreover, it is able to detect structural changes in the LV myocardium, including replacement fibrosis with the late gadolinium technique and expansion of the extracellular volume using T1 mapping (5). The latter in part reflects increases in diffuse myocardial fibrosis (a reversible early form of fibrosis) (6) and potential changes in the intravascular compartment. Early studies have suggested that CMR-derived measures of LV mass and replacement myocardial fibrosis are of prognostic significance (7,8). However, these studies have largely been conducted in small cohorts of patients with end-stage aortic stenosis who were referred to CMR on clinical grounds. Therefore, these findings may have been confounded by referral bias, which limited their applicability and generalizability to the broad population of patients with aortic stenosis. Moreover, comparisons with age- and sex-matched control populations and prognostic T1 mapping studies have been lacking.

We report the largest prospective study to evaluate systematically the usefulness of CMR in patients with aortic stenosis. In particular, we investigated its ability to detect expansion of extracellular volume (ECV) and replacement myocardial fibrosis, and how these are related to other markers of LV decompensation, functional capacity, and clinical outcomes.

METHODS

STUDY POPULATION. All stable patients with at least mild aortic stenosis (aortic jet velocity ≥2 m/s) who attended the Edinburgh Heart Centre between March 2012 and August 2014 were invited to participate in this prospective observational cohort study. The exclusion criteria were other forms of valvular heart disease (≥ moderate severity), significant comorbidities with limited life expectancy, contraindications to gadolinium-enhanced CMR, and acquired or inherited nonischemic cardiomyopathies (as assessed by clinical history or ultimately by CMR). In addition, we recruited healthy volunteers from the community with similar demographic characteristics in terms of age and sex, but no history or clinical features consistent with current cardiovascular disease. The study was conducted in accordance with the Declaration of Helsinki and approved by the local research committee. Written informed consent was obtained from all participants.

SUBJECT CHARACTERIZATION. All subjects underwent detailed clinical evaluation including history, physical examination, and electrocardiography. In addition, venous blood samples were obtained for evaluation of biochemistry and cardiac biomarkers of interest.

Cardiac biomarkers. Plasma cardiac troponin I concentrations (cTnI) were determined by the ARCHITECT STAT high-sensitivity cTnI assay (Abbot Laboratories, Abbott Park, Illinois) (9). The brain natriuretic peptide (BNP) concentration was determined with Triage BNP assay (Biosite Inc., San Diego, California).

6-min walk test. A 6-min walk test was performed in 156 (94%) patients as an objective measure of functional capacity in our predominantly older adult cohort, many of whom could not perform an exercise tolerance test. Explicit instructions were given to patients asking them to walk as far as possible for 6 min.

Echocardiography. Comprehensive transthoracic echocardiography was performed in all patients (iE33, Philips Medical Systems, the Netherlands) by a dedicated research ultrasonographer (A.C.W.) and a cardiologist certified in echocardiography (C.W.L.C.). The severity of aortic stenosis and diastolic function were assessed according to American Society of Echocardiography (ASE) guidelines (Online Appendix).

Cardiac magnetic resonance. CMR was performed using a 3-T scanner (MAGNETOM Verio, Siemens AG, Erlangen, Germany). Short-axis cine images were acquired and used to calculate ventricular volumes,