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Myocardial Extracellular Remodeling Is Associated With Ventricular Diastolic Dysfunction in Children and Young Adults With Congenital Aortic Stenosis

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Objectives This study sought to analyze cardiac magnetic resonance (CMR) measurements of myocardial extracellular volume fraction (ECV) and late gadolinium enhancement (LGE) in children and young adults with congenital aortic stenosis (AS) to determine the extent of fibrosis and examine their association with aortic valve and ventricular function.

Background Patients with congenital AS frequently have impaired diastolic ventricular function and exercise capacity that may be related to myocardial fibrosis.

Methods A total of 35 patients with congenital AS (median age 16 years) and 27 normal control subjects (median age 16 years) were evaluated by CMR. ECV was calculated from pre- and post-gadolinium contrast T1 measurements of blood and myocardium, and the hematocrit.

Results ECV was significantly higher in AS patients than in normal subjects (median 0.27 [range 0.22 to 0.42] vs. 0.25 [range 0.18 to 0.27], $p = 0.001$). LGE was present in 8 (24%) of the AS patients. A higher ECV was correlated with echocardiographic indexes of diastolic dysfunction including a higher mitral E-wave z-score ($r = 0.58$, $p = 0.002$), E/septal E′ z-score ($r = 0.56$, $p = 0.003$), E/mean E′ z-score ($r = 0.55$, $p = 0.003$), and indexed left atrial volume ($r = 0.56$, $p = 0.001$). Other factors associated with an elevated ECV (>0.28) included a greater number of aortic valve interventions ($p = 0.004$) and a greater number of aortic valve balloon valvuloplasties ($p = 0.003$). ECV was not significantly associated with AS gradient, left ventricular mass, mass/volume ratio, or ejection fraction.

Conclusions In young patients with AS, myocardial ECV is significantly elevated compared with control subjects and is associated with echocardiographic indexes of diastolic dysfunction. ECV measured by CMR may be a useful method for risk stratification and monitoring therapies targeting fibrosis. (J Am Coll Cardiol 2014;63:1778–85) © 2014 by the American College of Cardiology Foundation

Congenital aortic stenosis (AS) is a difficult disease to treat and requires lifelong attention. Although surgical and percutaneous therapy results in effective acute relief of obstruction, progressive stenosis or regurgitation is common, with a significant risk for multiple reinterventions on the aortic valve over a lifetime (1). These procedures are often performed with the aim of preserving systolic function. However, even in patients with adequate relief of obstruction, diastolic dysfunction and reduced exercise capacity are common (2,3). These impairments may be related to abnormalities in the myocardial extracellular matrix. Analysis

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of post-mortem specimens in patients with congenital AS has shown myocardial fibrosis (4), but little is known about its prevalence in vivo, evolution, and effect on ventricular function. An improved understanding of fibrosis in this condition may lead to novel management strategies directed more broadly at preservation of myocardial health.

For over a decade, the cardiovascular magnetic resonance (CMR) late gadolinium enhancement (LGE) technique has

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been used to detect focal regions of myocardial fibrosis (5). More recently, a CMR technique based on measurements of T1 relaxation times before and after gadolinium administration has been developed to determine the myocardial extracellular volume fraction (ECV) in order to assess diffuse fibrosis (6,7). ECV by this technique correlates with myocardial collagen fraction quantified by histopathology in murine hypertension models (8,9) and in adults with AS (10).

These CMR techniques provide an avenue of insight into the pathophysiology of congenital AS that has yet to be explored. Accordingly, the goals of this study were to use the newly-developed CMR measurement of myocardial ECV as well as LGE to determine the prevalence and extent of myocardial fibrosis in children and young adults with congenital AS, and to examine the association of ECV and LGE with parameters of left ventricular (LV) systolic and diastolic function, aortic valve function, exercise capacity, and clinical history.

Abbreviations and Acronyms

AS = aortic stenosis

CMR = cardiac magnetic resonance

ECV = extracellular volume fraction

LA = left atrial

LGE = late gadolinium enhancement

LV = left ventricular

PCWP = pulmonary capillary wedge pressure

Methods

Subjects. A retrospective database search identified all AS subjects who fulfilled the following criteria: 1) had a CMR examination at Boston Children's Hospital with a myocardial ECV measurement; 2) were <30 years of age; and 3) had congenital AS with an echocardiographic peak Doppler gradient ≥20 mm Hg at any time prior to the CMR examination. Subjects with aortic regurgitation or with a history of surgical or catheter interventions on the aortic valve were included. Demographic, clinical, and procedural data were abstracted from the medical record.

Control subjects came from Boston Children's Hospital and from the University Hospital of Schleswig-Holstein, Kiel, Germany. In Boston, a retrospective database search identified 22 patients who underwent a CMR examination with a myocardial ECV measurement, were <30 years of age, had a normal CMR examination, and had no history of left-sided heart disease or cardiomyopathy. In Kiel, 5 control subjects were recruited prospectively from among patients scheduled to undergo clinically-indicated brain magnetic resonance imaging with administration of a gadolinium-based contrast agent. They were all <30 years of age, had a normal CMR examination, and had no history of left-sided heart disease or cardiomyopathy.

The study protocol was approved by the Institutional Review Boards at Boston Children's Hospital and at University Hospital of Schleswig-Holstein.

Cardiac magnetic resonance. CMR examinations in AS and control subjects were performed on a 1.5-T scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands). Young patients who were unable to cooperate sufficiently were examined under general anesthesia.

T1 measurements for ECV calculation were obtained using a previously-described Look-Locker technique with bolus contrast administration (7). This approach was selected because its accuracy and reproducibility have been established (11). Moreover, compared with a modified Look-Locker inversion recovery approach (12), this technique has more complete sampling of the T1 recovery curve and is potentially less affected by heart rate (13). The latter point was particularly important because a relatively broad range of heart rates was expected, given that both pediatric and adult subjects are referred for CMR studies. An electrocardiogram-gated breath-hold Look-Locker sequence with a segmented gradient echo cine acquisition was performed at a single midventricular short-axis slice once prior to contrast administration and 3 times following contrast (5-min post-contrast, 10-min post-contrast, and at the end of the examination). Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) was used for contrast, with a bolus dose of 0.2 mmol/kg for patients <20 kg and 0.15 mmol/kg for patients ≥20 kg. Signal intensity versus time curves were generated for 6 equal sectors of the LV myocardium and the blood pool using commercially-available software (QMASS MR, Medis Medical Imaging Systems, Leiden, the Netherlands). Myocardium with LGE was excluded from the region of interest. From these curves, the T1 values were calculated by fitting to an analytical expression for the inversion recovery signal intensity. The myocardial R1 (R1 = 1/T1) was plotted against the blood pool R1. The slope of this relationship defines the partition coefficient for gadolinium (λ) (8). The myocardial ECV was then computed using the following equation: ECV = λ(1 − hematocrit expressed as a fraction) (7).

LGE imaging was performed 15 min after contrast administration using a standard 2-dimensional breath-hold phase-sensitive inversion recovery sequence with the inversion time selected to null the myocardial signal. Images were acquired in multiple long- and short-axis ventricular planes to encompass the entire myocardium. The images were later systematically reviewed, and the number of enhancing LV segments (17-segment model) and the pattern (full thickness, mid-wall, subendocardial, subepicardial) were recorded.

LV end-diastolic volume, end-systolic volume, ejection fraction, and mass were measured from a stack of cine steady-state free precession short-axis images in a standard fashion (14). Left atrial (LA) volume was calculated from horizontal and vertical long-axis ventricular views using the biplane area-length method (15).

Echocardiography. The echocardiogram closest in time to the CMR examination was reviewed for each subject. Pulsed-wave and tissue Doppler parameters were measured 3 times by a single observer, averaged, and converted to z-scores to adjust for the effect of age. Age-based normative values were