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ORIGINAL RESEARCH

Myocardial Extracellular Volume Expansion and the Risk of Recurrent Atrial Fibrillation After Pulmonary Vein Isolation

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OBJECTIVES This study tested whether myocardial extracellular volume (ECV) is increased in patients with hypertension and atrial fibrillation (AF) undergoing pulmonary vein isolation and whether there is an association between ECV and post-procedural recurrence of AF.

BACKGROUND Hypertension is associated with myocardial fibrosis, an increase in ECV, and AF. Data linking these findings are limited. T_1 measurements pre-contrast and post-contrast in a cardiac magnetic resonance (CMR) study provide a method for quantification of ECV.

METHODS Consecutive patients with hypertension and recurrent AF referred for pulmonary vein isolation underwent a contrast CMR study with measurement of ECV and were followed up prospectively for a median of 18 months. The endpoint of interest was late recurrence of AF.

RESULTS Patients had elevated left ventricular (LV) volumes, LV mass, left atrial volumes, and increased ECV (patients with AF, 0.34 ± 0.03; healthy control patients, 0.29 ± 0.03; $p < 0.001$). There were positive associations between ECV and left atrial volume ($r = 0.46$, $p < 0.01$) and LV mass and a negative association between ECV and diastolic function (early mitral annular relaxation [E′], $r = -0.55$, $p < 0.001$). In the best overall multivariable model, ECV was the strongest predictor of the primary outcome of recurrent AF (hazard ratio: 1.29; 95% confidence interval: 1.15 to 1.44; $p < 0.0001$) and the secondary composite outcome of recurrent AF, heart failure admission, and death (hazard ratio: 1.35; 95% confidence interval: 1.21 to 1.51; $p < 0.0001$). Each 10% increase in ECV was associated with a 29% increased risk of recurrent AF.

CONCLUSIONS In patients with AF and hypertension, expansion of ECV is associated with diastolic function and left atrial remodeling and is a strong independent predictor of recurrent AF post–pulmonary vein isolation. (J Am Coll Cardiol Img 2014;7:1–11) © 2014 by the American College of Cardiology Foundation

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Systemic arterial hypertension (HTN) is one of the most common risk factors for the development of atrial fibrillation (AF) (1). An early myocardial response in adjustment to pressure overload in HTN is an increase in the myocardial extracellular volume (ECV) due to the development of pathological myocardial fibrosis (2). Myocardial fibrosis is associated with myocardial stiffening, diastolic dysfunction, and elevated left atrial (LA) pressure, which are all key factors involved in the development of AF. However, there are limited data directly linking myocardial fibrosis with AF (3,4), and data suggest that myocardial fibrosis in HTN is potentially reversible, especially at an early stage (5). The gold standard for detection of myocardial fibrosis, endomyocardial biopsy, is invasive. The current optimal noninvasive test for detection of replacement myocardial fibrosis, such as that which occurs with a myocardial infarction, is cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) (6). However, LGE-CMR depends on focal contrast enhancement relative to a normal area of myocardium. Disease processes such as HTN are likely diffuse and lack a normal reference myocardium (7). Consistent with this are published data on the presence of LGE in patients with HTN, ranging from 0% to approximately 50% (8,9), underestimating both the presence and extent of fibrosis suggested by pathological data (10–12).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CI = confidence interval
CMR = cardiac magnetic resonance
ECG = electrocardiography
ECV = extracellular volume
HR = hazard ratio
HTN = hypertension
LA = left atrial
LGE = late gadolinium enhancement
LV = left ventricular
PVI = pulmonary vein isolation

These limitations have prompted research into novel CMR-based quantitative techniques for measurement of myocardial ECV. The ECV derived using a contrast CMR study is derived from pre-contrast and post-contrast T_1 measurements (13–17), has been validated as a noninvasive estimate of myocardial fibrosis (15,17), and an elevated ECV is associated with increased mortality (18). However, there are limited data on whether the ECV derived by CMR is abnormal in patients with HTN (19); furthermore, there are limited data linking expansion of ECV with adverse clinical outcomes (18). However, a study testing a broad group of patients with HTN for both expansion of ECV and linking expansion of ECV in patients with isolated HTN to adverse events requires preliminary data. Before pulmonary vein isolation (PVI), we routinely perform imaging of pulmonary vein anatomy with CMR, and HTN is one of the primary etiologies of AF in patients requiring PVI. Therefore, we tested whether T_1 measurements could detect expansion of ECV in patients with HTN undergoing PVI for treatment of recurrent AF, whether the ECV in this population was associated with other measures of cardiovascular structure and function, and whether an elevated ECV in this population was associated with risk of recurrent AF after PVI.

METHODS

Study population. We performed a prospective observational study of consecutive patients with HTN undergoing PVI for treatment of recurrent AF. The cohort underwent CMR that included gadolinium between July 2009 and January 2012. Patients were referred for a CMR study specifically for imaging of pulmonary veins before PVI for treatment of recurrent AF. We choose this population for 2 reasons: the incidence of isolated HTN is high among patients with AF, and patients scheduled to undergo PVI for treatment of AF are routinely referred for CMR-based imaging of the pulmonary veins at our institution. To limit the contribution of other pathologies that expand myocardial ECV, we excluded patients with diabetes mellitus, myocardial infarction (by either history according to the presence of pathological Q-waves on electrocardiography [ECG] or a typical LGE infarct pattern), severe renal failure (glomerular filtration rate <30 ml/m^2), a history of heart failure or any prior documented reduced left ventricular ejection fraction ($<50\%$), significant valvular heart disease (greater than moderate aortic stenosis,

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