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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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## Atrial Dysfunction Assessed by Cardiac Magnetic Resonance as an Early Marker of Fabry Cardiomyopathy

Anderson-Fabry disease (AFD) cardiomyopathy is characterized by glycosphingolipid (Gb3) storage in all cellular components, with consequent left ventricular hypertrophy (LVH). Gb3 accumulation also involves atrial myocytes (1), ultimately leading to left atrial (LA) enlargement and reduced atrial compliance. Cardiac magnetic resonance (CMR) plays an important role in the assessment of the severity of Fabry cardiomyopathy. CMR feature tracking (CMR-FT) specifically allows the assessment of myocardial strain from cine images (2).

Previous studies investigated LA strain in AFD by speckle-tracking echocardiography but did not explore the relationship between LA dysfunction and severity of LV involvement (3). We aimed to evaluate whether LA impairment may precede LV remodeling, representing an expression of atrial myopathy related to Gb3 accumulation.

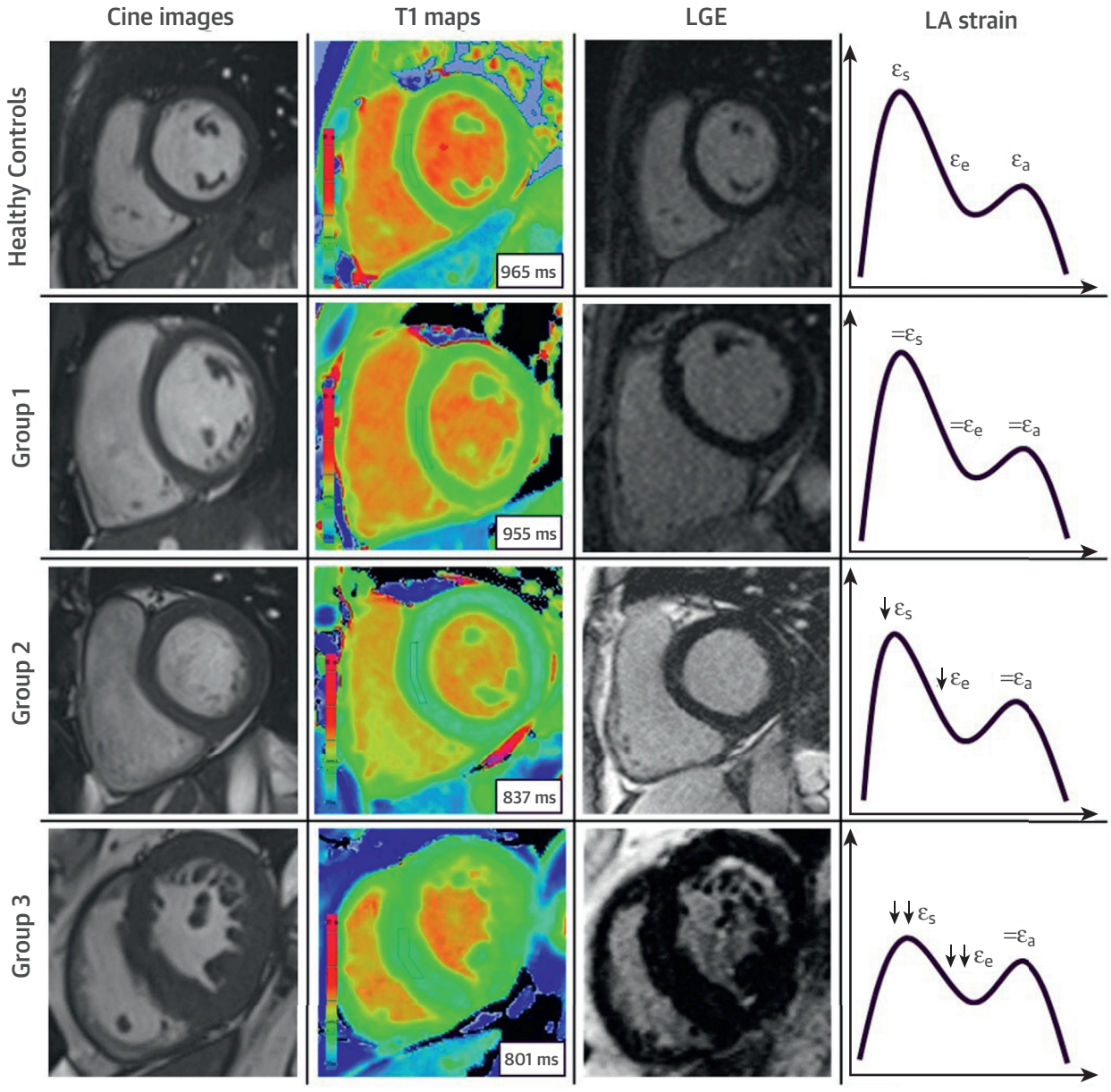
In this retrospective, observational study, 45 patients with AFD underwent CMR with T1 mapping using shortened modified Look-Locker inversion recovery sequences, 2-dimensional echocardiography, and quantification of Mainz Severity Score Index (MSSI). Patients were divided into 3 groups (n = 15 each) with increasing severity: 1) normal T1, no LVH; 2) low T1, no LVH; and 3) LVH. Patients were compared with 15 healthy control subjects. CMR-FT was applied for the analysis of LA strain (total, conduit, booster) and volumes.

Mean age of the patients with AFD was 38.5 ± 15.1 years; there were 34 (56%) men. No differences in sex distribution and "classic" mutation prevalence were found between groups. Higher values of global or cardiovascular MSSI, rate of patients assuming enzyme replacement therapy, indexed LV mass, LV maximum wall thickness, and late gadolinium enhancement-positive segments were observed from groups 1 to 3, reflecting a gradient of disease severity. Native T1 values were normal in healthy control subjects and in group 1 patients and were progressively lower in group 2 and 3.

LA total strain was comparable between control subjects and patients in group 1 (36.8 ± 6.4% vs. 36.8 ± 6.0%; $p = 0.45$), while a significant difference was found between group 1 and group 2 (36.8 ± 6.4% vs. 29.9 ± 5.2%; $p = 0.01$). Group 3 showed a significantly reduced LA total strain compared with all other groups (19.6 ± 4.8%; $p < 0.001$ for all). A progressive reduction in LA conduit strain was observed from control subjects to group 3, paralleling the increase in patients with echocardiographic diastolic dysfunction. No difference among groups was found in LA booster strain values (**Figure 1**). Atrial volumes were significantly increased in group 3 compared with the other groups. Overall, LA total strain showed very good correlation with native septal T1, LV maximum wall thickness, atrial volumes, and global or cardiovascular MSSI. Univariate regression analysis showed a significant association between LA total strain and age, native septal T1, and MSSI but not with sex or presence of "classic" mutations.

This is the first study systematically assessing LA function by CMR-FT in a population of patients with AFD stratified according to the degree of LV involvement. Atrial deformation was already impaired in patients with AFD with low T1 values (tracking Gb3 deposition), even in the absence of LVH and diastolic dysfunction. This is consistent with the concept of an atrial myopathy directly caused by Gb3 deposition, primarily affecting atrial compliance. Glycosphingolipid storage in the atrial myocardium has been previously reported in histological studies, regardless of LVH or enzyme replacement therapy (1,4). As observed in hypertrophic cardiomyopathy, atrial myopathy in AFD seems to affect primarily LA

**FIGURE 1** **LA Strain in Different Stages of Anderson-Fabry Disease Cardiomyopathy**




Moving from control subjects to group 3, a progressive reduction in left atrial (LA) total strain ($\varepsilon_s$) and conduit strain ($\varepsilon_e$) with lowering of T1 values and increase of left ventricular mass can be observed. LA booster strain ($\varepsilon_a$) is preserved also in the last stages of cardiomyopathy. LGE = late gadolinium enhancement.

compliance rather than atrial contractility. The atrial myopathy appears to progress in parallel with the ventricular features of AFD cardiomyopathy as well as its extracardiac manifestations, regardless of male sex or presence of a classic mutation. In particular, a good correlation was found with native T1 values, which in pre-hypertrophic patients with AFD had been shown to provide prognostic information (5).

In conclusion, this study contributes to the characterization of the pre-hypertrophic phenotype of AFD, introducing LA total strain as a potential novel

indicator of early cardiac involvement and a possible tool to personalize management decisions in these patients.

This study received approval from the local research ethics committee, and all participants provided written informed consent.

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# Ischemic Myocardial Burden Subtended by Computed Tomography–Derived Fractional Flow Reserve ($APPROACH_{FFRCT}$)

## An Exploratory Analysis on Diagnostic Performance

Fractional flow reserve derived from coronary computed tomography angiography ($FFR_{CT}$) is an emerging noninvasive modality that accurately identifies ischemic vessels (1), although recent evidence suggests that gray-zone $FFR_{CT}$ values between 0.70 to 0.80 are associated with only modest diagnostic accuracy. The ischemic myocardial burden is an established metric used to guide clinical decision making and is traditionally assessed using noninvasive stress imaging. The potential to incorporate $FFR_{CT}$ values ("depth" of ischemia), together with CT-derived ischemic myocardial burden ("extent" of ischemia), has yet to be explored and may improve the diagnosis of hemodynamically significant coronary stenosis. Therefore, the aim of this study was to evaluate the incremental diagnostic performance of $FFR_{CT}$-defined ischemic myocardial burden when compared with $FFR_{CT}$ alone in $FFR_{CT}$ significant vessels (≤0.80).

This is a subanalysis of the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial, a prospective study of stable coronary artery disease patients undergoing CT angiography, $FFR_{CT}$, and FFR (1). We included 109 patients and 181 vessels with $FFR_{CT}$ ≤0.80 (mean age 63.0 ± 9.7 years; 75% men). Burden of ischemic myocardium was defined as percentage of left ventricular myocardium subtended beyond the point at which the vessel $FFR_{CT}$ becomes ≤0.80, as estimated by the APPROACH ($APPROACH_{FFRCT}$) score (**Figures 1A to 1C**). The APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) score is a cardiac magnetic resonance–validated scoring matrix providing an anatomic estimate of the myocardial territory at risk based on vessel