

*Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, Massachusetts 02215
E-mail: wmanning@bidmc.harvard.edu
<https://doi.org/10.1016/j.jcmg.2020.05.006>

© 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors thank Stephanie Li and the BIDMC Centers for Healthcare Delivery Science for assisting with creation of the demographic portion of our database.

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.

REFERENCES

1. Satish M, Walters RW, Alla VM. Trends in use of echocardiography in hospitalized patients with syncope. *Echocardiography* 2019;36:7-14.
2. Papolos A, Narula J, Bavishi C, Chaudhry FA, Sengupta PP. U.S. hospital use of echocardiography. *J Am Coll Cardiol* 2016;67:502-11.
3. Shen W-K, Sheldon R, Benditt D, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *J Am Coll Cardiol* 2017;70:2102-4]. *J Am Coll Cardiol* 2017;70:e39-110.

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,

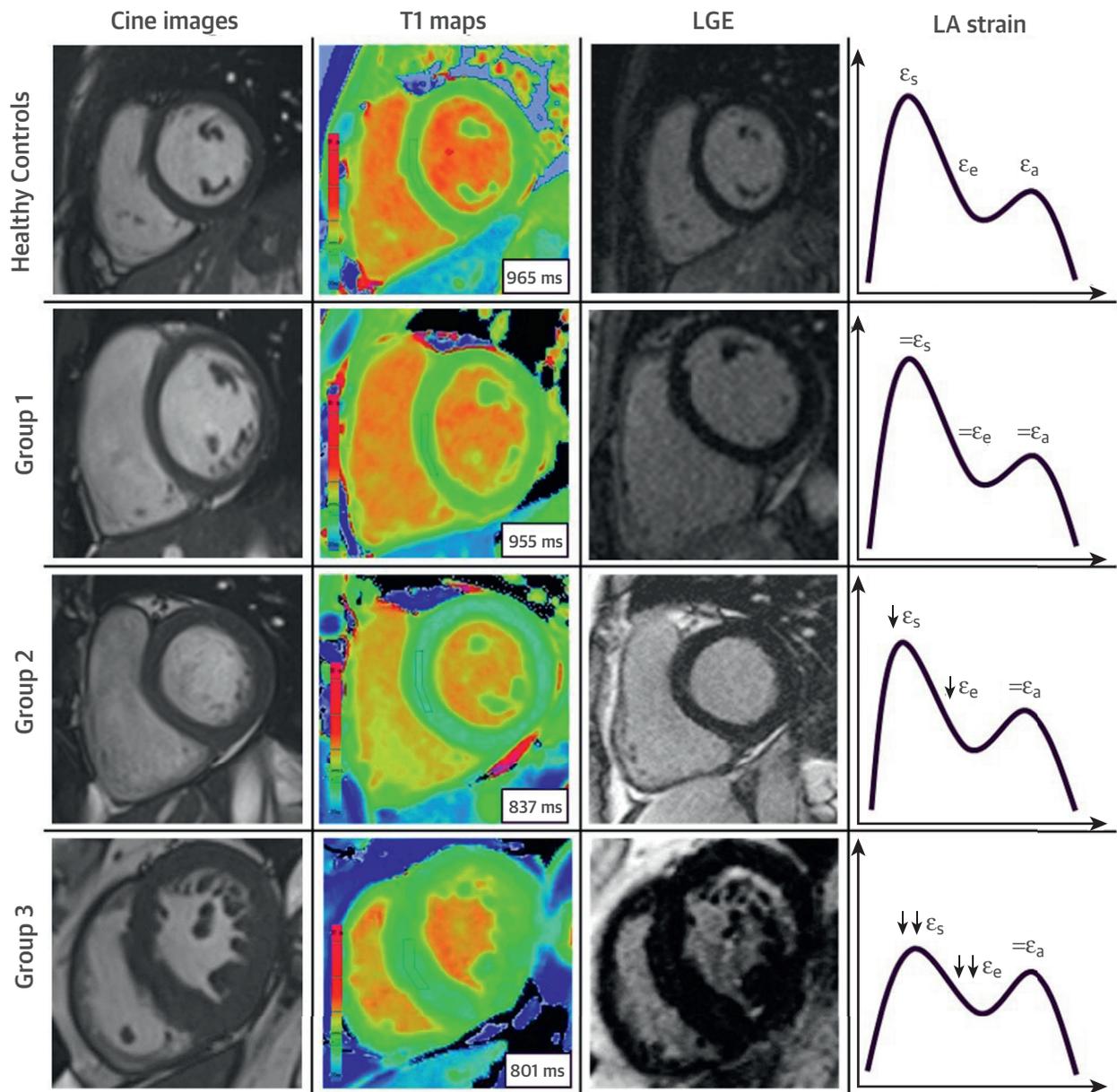
and quantification of Mainz Severity Score Index (MSSI). Patients were divided into 3 groups (n = 15 each) with increasing severity: 1) normal T1, no LVH; 2) low T1, no LVH; and 3) LVH. Patients were compared with 15 healthy control subjects. CMR-FT was applied for the analysis of LA strain (total, conduit, 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 ($36.8 \pm 6.4\%$ vs. $36.8 \pm 6.0\%$; $p = 0.45$), while a significant difference was found between group 1 and group 2 ($36.8 \pm 6.4\%$ vs. $29.9 \pm 5.2\%$; $p = 0.01$). Group 3 showed a significantly reduced LA total strain compared with all other groups ($19.6 \pm 4.8\%$; $p < 0.001$ 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 (ϵ_e) and conduit strain (ϵ_e) with lowering of T1 values and increase of left ventricular mass can be observed. LA booster strain (ϵ_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.

Andrea Bernardini, MD[†]*

Antonia Camporeale, MD, PhD[†]

Maurizio Pieroni, MD, PhD

Federico Pieruzzi, MD, PhD

Stefano Figliozzi, MD

Paola Lusardi, MD

Marco Spada, MD

Renzo Mignani, MD

Alessandro Burlina, MD

Francesca Carubbi, MD

Yuri Battaglia, MD

Francesca Graziani, MD, PhD

Silvia Pica, MD

Lara Tondi, MD

Kelvin Chow, PhD

Sara Boveri, MSc

Iacopo Olivotto, MD

Massimo Lombardi, MD

*Multimodality Imaging Section

IRCCS Policlinico San Donato

Via Morandi 30

20097 San Donato

Italy

E-mail: andrea.bernardini@grupposandonato.it

<https://doi.org/10.1016/j.jcmg.2020.05.011>

© 2020 by the American College of Cardiology Foundation. Published by Elsevier.

Please note: †Drs. Bernardini and Camporeale contributed equally to this work. This study was partially supported by Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato. Dr. Camporeale has received honoraria for presentations and board meetings from Amicus Therapeutics, Sanofi-Genzyme, and Shire; and research grant support from Amicus Therapeutics. Dr. Pieroni has received speaker and advisory board honoraria and travel support from Sanofi-Genzyme, Amicus Therapeutics, and Shire. Dr. Pieruzzi has received honoraria from Sanofi-Genzyme, Shire, and Amicus Therapeutics. Dr. Spada has received honoraria for speaker fees for symposia and meetings and for advisory board attendance from Sanofi Genzyme and Shire International. Dr. Migani has received honoraria from and served as an expert witness for Sanofi-Genzyme and Amicus Therapeutics. Dr. Burlina has received honoraria for presentations and board meetings from Amicus Therapeutics and Sanofi Genzyme; and served on the European Advisory Board of the Fabry Registry, which is sponsored by Genzyme. Dr. Carubbi has received travel reimbursement and lecture and advisory board honoraria from Sanofi, Shire, Amicus, Amgen, and Mylan. Dr. Graziani has received travel honoraria from Genzyme, Shire, and Amicus; and speaker honoraria from Shire and Genzyme. Dr. Chow is a full-time employee of Siemens Medical Solutions USA. Dr. Olivotto has received research grant support and honoraria from Sanofi-Genzyme, Shire, Bayer, and MyoKardia. Dr. Lombardi has received honoraria from Shire. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. 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](#).

REFERENCES

1. Chimentì C, Russo MA, Frustaci A, et al. Atrial biopsy evidence of Fabry disease causing lone atrial fibrillation. *Heart* 2010;96:1782-3.

2. Evin M, Cluzel P, Lamy J, et al. Assessment of left atrial function by MRI myocardial feature tracking. *J Magn Reson Imaging* 2015;42:379-89.

3. Pichette M, Serri K, Pagé M, et al. Impaired left atrial function in Fabry disease: a longitudinal speckle-tracking echocardiography study. *J Am Soc Echocardiogr* 2017;30:170-9.e2.

4. Sheppard MN, Cane P, Florio R, et al. A detailed pathologic examination of heart tissue from three older patients with Anderson-Fabry disease on enzyme replacement therapy. *Cardiovasc Pathol* 2010;19:293-301.

5. Camporeale A, Pieroni M, Pieruzzi F, et al. Predictors of clinical evolution in prehypertrophic Fabry disease. *Circ Cardiovasc Imaging* 2019;12:e008424.

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