

## Extracellular Volume Imaging and Quantitative T2 Mapping for the Diagnosis of Mitochondrial Cardiomyopathy

Kyoung Hwa Lee, Heae Surng Park, Chul Hwan Park, Ki-Hyun Kim, Hyemoon Chung, Tae Hoon Kim, Se-Joong Rim and Eui-Young Choi

*Circulation*. 2014;130:1832-1834

doi: 10.1161/CIRCULATIONAHA.114.010779

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2014 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/130/20/1832>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>

## Extracellular Volume Imaging and Quantitative T2 Mapping for the Diagnosis of Mitochondrial Cardiomyopathy

Kyoung Hwa Lee, MD; Heae Surng Park, MD; Chul Hwan Park, MD; Ki-Hyun Kim, MD; Hyemoon Chung, MD; Tae Hoon Kim, MD, Se-Joong Rim, MD; Eui-Young Choi, MD

A 39-year-old woman visited an outpatient clinic complaining of nausea and vomiting for 1 week. She had been experiencing dyspepsia for several months. Her endoscopic gastroduodenography did not show any remarkable findings. She was lean and of short stature, with a weight of 29 kg, height of 147 cm, and an approximated body mass index of 13.49 kg/m<sup>2</sup>. She had some hearing difficulties and cognitive dysfunction. Her parents died when she was a teenager; her mother passed away because of diabetic complications in her third decade. She was a nonsmoker and denied any history of hypertension or symptoms of chest pain except for alleged diabetes mellitus. Her chest x-ray film showed cardiomegaly, and ECG revealed normal sinus rhythm and left ventricular hypertrophy with T-wave inversion along V4~6 precordial lead. Her blood troponin-T and creatine kinase MB levels were mildly elevated. Lactate dehydrogenase and B-type natriuretic peptide levels were also elevated to 456 IU/L and 147.0 pg/mL, respectively. Her hemoglobin A1C level was elevated, whereas Islet cell antibody and insulin antibody levels were normal, suggesting type 2 diabetes mellitus. On pure tone audiometry, sensory neural hearing loss at 2 kHz was noted in both ears: 70 dB in the right ear and 50 dB in the left. Transthoracic echocardiogram showed normal-sized cardiac chambers and severely reduced global left ventricular systolic function, with an estimated ejection fraction of 35% and a small amount of pericardial effusion. The left ventricular wall was thickened, and grade-2 diastolic dysfunction was noted (Figure 1). To characterize the myocardium, cardiac MRI was performed, revealing a diffusely increased T2 value of 68 ms on T2 map. However, no late gadolinium enhancement (LGE) was noted. In the T1 mapping, precontrast and postcontrast T1 values were 1078 ms and 469 ms, respectively. The calculated extracellular volume fraction was 34%, suggesting extracellular space expansion (Figure 2), which implied a lower possibility of hypertrophic cardiomyopathy, cardiac amyloidosis, and infiltrative cardiomyopathy. Cardiac biopsy revealed vacuolar change in myocardial cells with minimal inflammatory infiltrate and perimysial fibrosis. Nevertheless,

severe lymphocyte infiltration suggesting acute or chronic myocarditis was not seen. Gomori trichrome stain showed ragged red fibers. On electron microscopic examination, the number of mitochondria was increased. Aberrant mitochondria with fingerprint arrangement or osmophilic body were present. The histopathologic findings were compatible with mitochondrial myopathy (Figure 3). In addition, her sampled blood mitochondrial DNA was analyzed by PCR sequencing, and m.3243A>G mutation, which is frequently detected in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, was detected (Figure 4.) Blood enzyme activity analysis results confirmed normal activity of  $\alpha$ - and  $\beta$ -galactosidase, suggesting no evidence of Fabry disease, Pompe disease, or Gauchers disease. Under the diagnosis of mitochondrial disease with gastrointestinal and myocardial involvement, the patient was given coenzyme Q10 and carnitine, in addition to an angiotensin-converting enzyme inhibitor.

In this case, a number of systemic findings associated with mitochondrial disease were noted, including short stature, cognitive dysfunction, both sensory neural hearing loss, type 2 diabetes mellitus with maternal heritage, gastrointestinal dysmotility attributable to autonomic dysfunction, and cardiomyopathy. Myocardial pathology of mitochondrial cardiomyopathy (MC) varies. Previous reports showed patterns of LGE can be helpful for obtaining information on myocardial tissue characteristics in MC.<sup>1,2</sup> In the present study, T1, T2 mapping, and extracellular volume fraction analysis provided additional information on myocardial tissue status in a case without LGE. The major role of cardiac MRI is to exclude any infiltrative cardiomyopathy or hypertrophic cardiomyopathy in cases with thickened myocardium. In this case, after echocardiography, Fabry disease, cardiac amyloidosis, or diffusely thickened hypertrophic cardiomyopathy should be differentiated from MC. Genetic study and systemic involvement are important for the diagnosis of MC. Findings of no patch LGE in septa and no subendocardial LGE combined with a diffuse increase in T2 suggested a lower possibility of hypertrophic cardiomyopathy or cardiac amyloidosis

From the Department of Internal Medicine, Division of Cardiology (K.H.L., K.-H.K., H.C., S.-J.R., E.-Y.C.), and the Departments of Pathology (H.S.P.) and Radiology (C.H.P., T.H.K.), Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

Correspondence to Eui-Young Choi, MD, PhD, Division of Cardiology, Heart Center, Gangnam Severance Hospital, Yonsei University College of Medicine 146-92 Dogok-dong, Gangnam-gu, Seoul 135-720, Korea. E-mail choi0928@yuhs.ac  
(*Circulation*. 2014;130:1832-1834.)

© 2014 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.114.010779

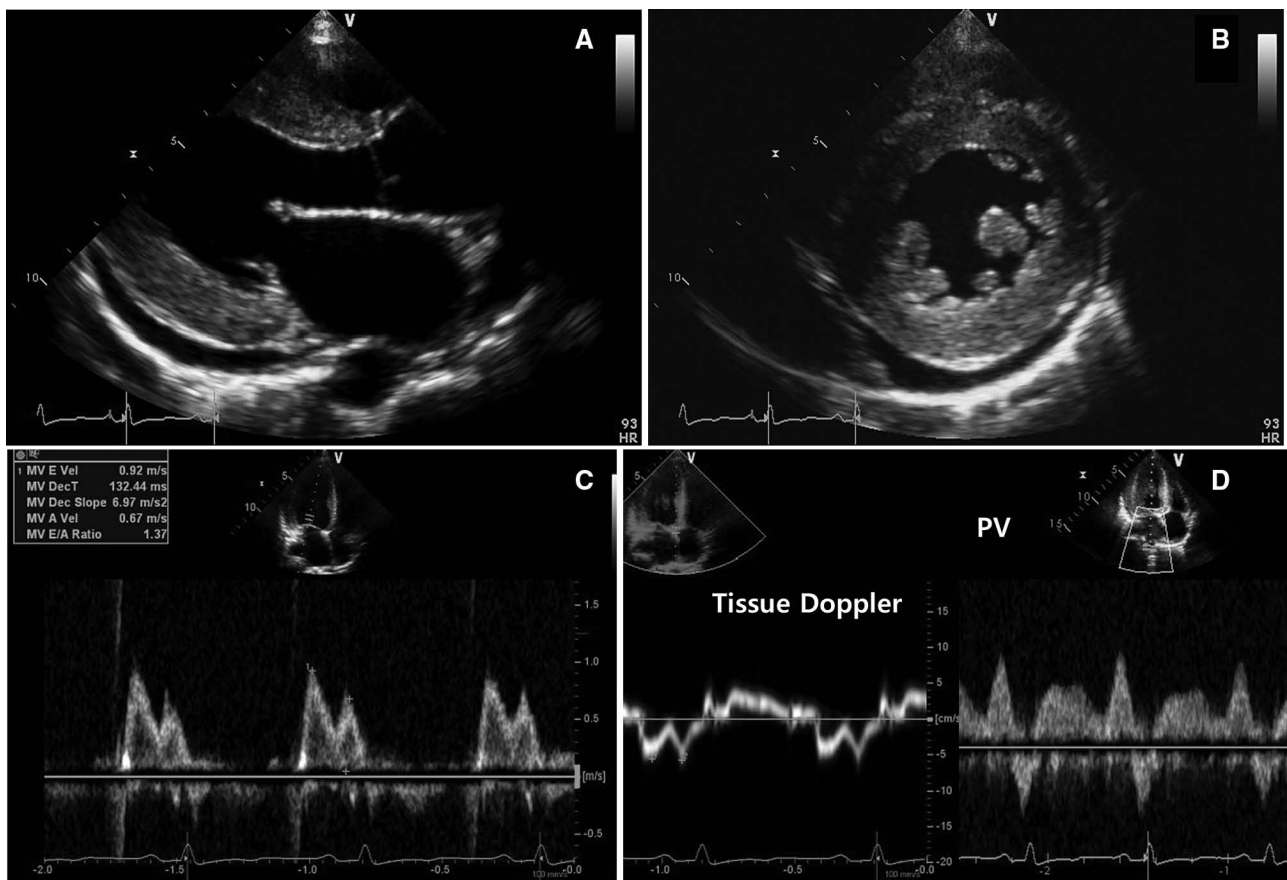
because T2 increase is not observed in these disease entities. No native T1 shortening was a clue to exclude Fabry disease and other glycogen storage disease.<sup>3</sup> Expansion of extracellular volume in a case without LGE was also informative because two-thirds of cases of MC do not show any LGE.<sup>4</sup> T2-weighted images are now challenged by several limitations. To overcome these limitations, direct quantification of T1 and T2 through a mapping technique is helpful. The patient described herein exhibited m.3243A>G mtDNA mutation, which can cause MELAS syndrome, in which T2 has been reported to be increased.<sup>4</sup> The T2 increase can be from myocardial edema to some degree or intracytoplasmic vacuole. Not only was clinically viral myocarditis not indicated in this case, but also the absence of subepicardial or midwall LGE in the absence of severe lymphocyte infiltration excluded acute or chronic myocarditis. Accordingly, such findings can provide clues to diagnosing MC.

## Disclosures

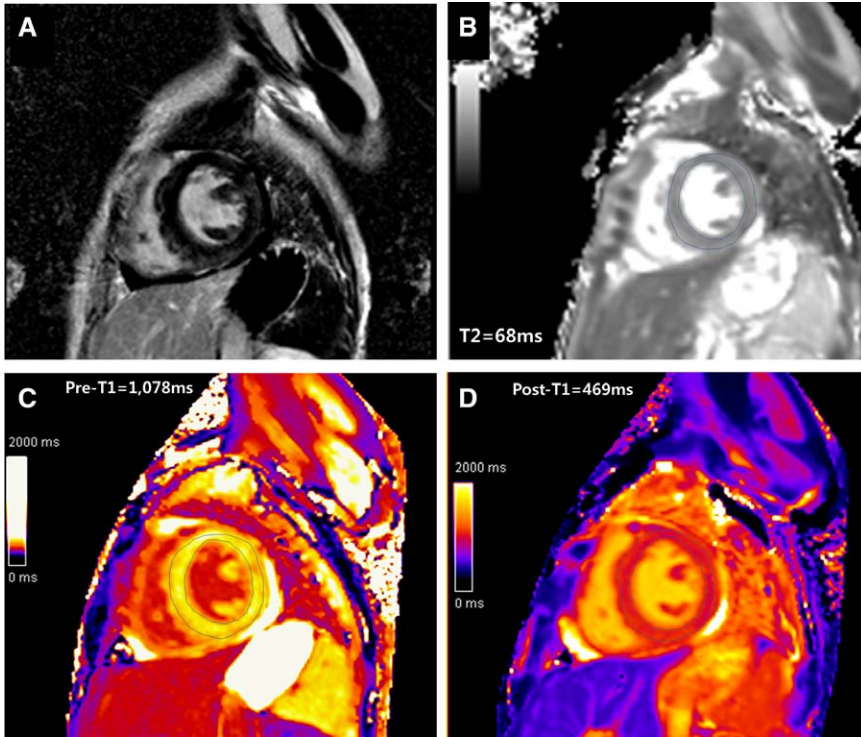
None.

## References

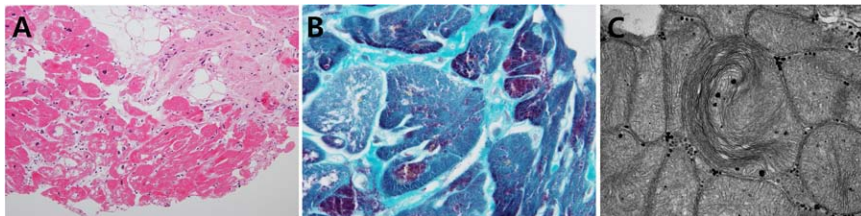
1. Partington SL, Givertz MM, Gupta S, Kwong RY. Cardiac magnetic resonance aids in the diagnosis of mitochondrial cardiomyopathy. *Circulation*. 2011;123:e227–e229.
2. Jose T, Gdynia HJ, Mahrholdt H, Vöhringer M, Klingel K, Kandolf R, Bornemann A, Yilmaz A. CMR gives clue to “ragged red fibers” in the heart in a patient with mitochondrial myopathy. *Int J Cardiol*. 2011;149:e24–e27.
3. Sado DM, White SK, Piechnik SK, Banyersad SM, Treibel T, Captur G, Fontana M, Maestrini V, Flett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neubauer S, Elliott PM, Moon JC. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. *Circ Cardiovasc Imaging*. 2013;6:392–398.
4. Yilmaz A, Gdynia HJ, Ponfick M, Rösch S, Lindner A, Ludolph AC, Sechtem U. Cardiovascular magnetic resonance imaging (CMR) reveals characteristic pattern of myocardial damage in patients with mitochondrial myopathy. *Clin Res Cardiol*. 2012;101:255–261.



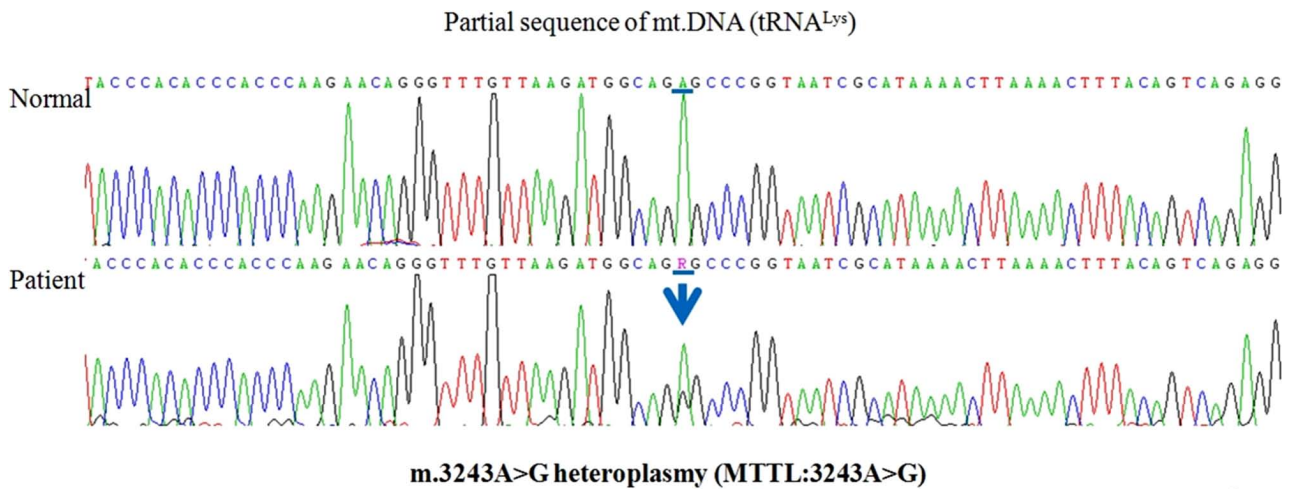
**Figure 1.** Parasternal long-axis (A) and short-axis (B) transthoracic echocardiography view shows thickened left ventricular myocardium with small pericardial effusion. Mitral inflow Doppler pattern (C) and tissue Doppler of mitral annulus and reversal of systolic and diastolic inflow pattern of pulmonic vein Doppler (D) suggest grade-2 diastolic dysfunction. PV indicates pulmonic vein.



**Figure 2.** Cardiac MRI findings. No late gadolinium enhancement (**A**) is noted. Measured T2 value in T2 map is increased by 68 ms (**B**). Precontrast (**C**) and postcontrast (**D**) T1 value in T1 map is 1078 ms and 469 ms, respectively, and then calculated extracellular volume fraction is increased by 34%. Region of interest placed on the entire myocardium.



**Figure 3.** Histopathologic findings of cardiac biopsy. **A**, Vacuolar change in myocardial cells and perimysial fibrosis, Hematoxylin and eosin,  $\times 200$ . **B**, Gomori trichrome stain showing ragged red fibers,  $\times 1000$ . **C**, Electron microscopy showing abnormal mitochondria with fingerprint arrangement,  $\times 50000$ .



**Figure 4.** Mitochondrial DNA PCR sequencing and m.3243A>G mutation.