

Trajectory of left ventricular geometry and diastolic dysfunction in hereditary transthyretin cardiac amyloidosis

Tatsuya Akatsuka¹, Naoki Fujimoto^{1*}, Masaki Ishiyama¹, Shiro Nakamori¹, Kyoko Imanaka-Yoshida² and Kaoru Dohi¹

¹Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan; and ²Department of Pathology and Matrix Biology, Mie University Graduate School of Medicine, Tsu, Japan

Abstract

Amyloid transthyretin (ATTR) depositions cause left ventricular (LV) hypertrophy, diastolic dysfunction, and heart failure. The time course of changes in LV geometry and diastolic dysfunction has not been fully reported in patients with ATTR cardiomyopathy. A 79-year-old woman with previous myocardial infarction presented with shortness of breath on exertion, and progressive bilateral lower extremity weakness and polyneuropathy. She was diagnosed with Val30Met hereditary ATTR cardiomyopathy by cardiac biopsy and genetic testing. During the past 5 year period, significant LV concentric remodelling with small LV cavity occurred, resulting in an increased LV stiffness and prolonged LV relaxation. This case report highlights the time course of changes in LV geometry and diastolic function and the importance of early diagnosis of ATTR cardiomyopathy.

Keywords Amyloid; Cardiac transthyretin amyloidosis; Pressure–volume relationships; Left ventricular function

Received: 23 December 2020; Revised: 31 March 2021; Accepted: 21 May 2021

*Correspondence to: Naoki Fujimoto, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Tel: +81-59-231-5015; Fax: +81-59-231-5201. Email: naokifujimo@clin.medic.mie-u.ac.jp

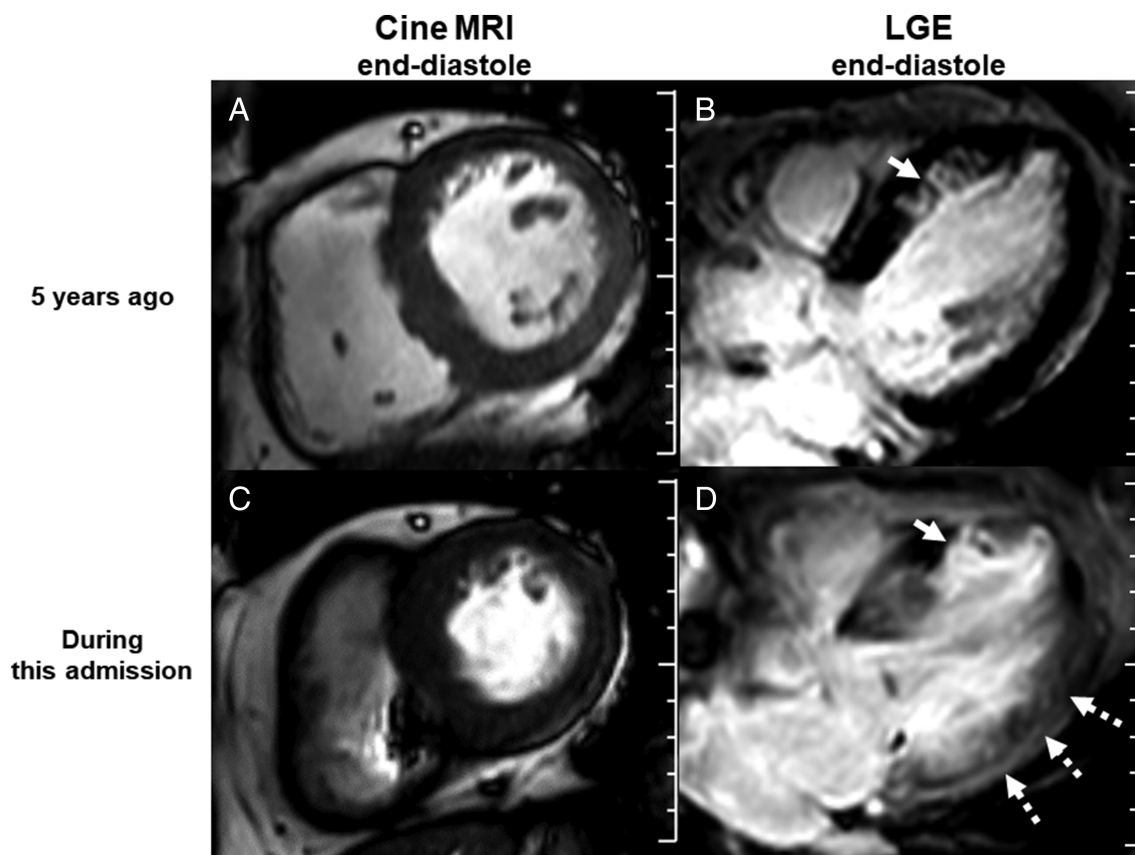
Case report

A 79-year-old woman with hypertension, insulin-dependent diabetes mellitus, and previous myocardial infarction (MI) was referred to our hospital for shortness of breath on exertion. She had a longer than 10 year history of carpal tunnel syndrome and cervical spondylosis. Five years prior to this admission, she had left anterior fascicular block, first-degree atrioventricular (AV) block, and heart failure due to silent subendocardial anteroseptal MI. She underwent staged percutaneous coronary intervention of the left anterior descending artery. Medications, including angiotensin-converting enzyme inhibitors and diuretics, for heart failure were added. Cardiac magnetic resonance imaging (MRI) in the chronic phase demonstrated normal left ventricular (LV) wall motion and subendocardial late gadolinium enhancement (LGE) only in the area damaged by the MI (Figure 1A and 1B). Two years before this admission, her conduction disturbance

progressed to advanced AV block and a DDD pacemaker was implanted. She noted progressive bilateral lower extremity dyskinesia and hand weakness with prickling and tingling sensations over the last few years. Her younger brother was recently diagnosed with hereditary amyloid transthyretin (ATTR).

On this admission, she was 154 cm in height and 49 kg in weight and had New York Heart Association Functional Class II symptoms. During the last 5 years, she had unintentional and progressive weight loss of 9 kg. Physical examination revealed no jugular venous distension or cardiac murmur, but muscle weakness and sensory deficits in the distal upper and lower extremities were observed. A slight increase in brain natriuretic peptide (BNP) level of 72.8 pg/mL was observed. Electrocardiography revealed an atrial–ventricular-paced rhythm with a heart rate of 60 b.p.m. A normal LV ejection fraction of 68%, diastolic dysfunction, enlarged left atrium, intraventricular septal thickness of 12 mm, and

Figure 1 Cine magnetic resonance imaging (MRI) (A) and late gadolinium enhancement (LGE) obtained 5 years ago showing subendocardial anteroseptal old myocardial infarction (B, arrow). Cine MRI showing a decreased left ventricular cavity size and increased left ventricular and right ventricular wall thickness over time (C). The presence of transmural LGE was detected in the lateral and posteroinferior walls (D, dashed arrow).



posterior wall thickness of 10 mm were observed on echocardiography. Relative apical sparing pattern of longitudinal strain was not observed probably because of the previous anteroseptal MI and right ventricular pacing. Compared with the previous MRI findings, a significantly smaller LV end-diastolic volume (70 vs. 145 mL) and greater LV mass (97 vs. 72 g) were noted on cardiac MRI. The LV mass–volume ratio increased from 0.50 to 1.39, suggesting concentric LV and right ventricular hypertrophy with a small LV cavity (Figure 1C). In addition to the previously documented anteroseptal LGE, the presence of subendocardial or transmural LGE was detected in the lateral and posteroinferior walls (Figure 1D). Global native T1 was prolonged (1446 ms; our normal, 1294 ± 39 ms), and the global extracellular volume was 49.2%. ^{99m}Tc -Pyrophosphate scintigraphy demonstrated Grade 3 accumulation in the myocardium. Myocardial biopsy from the right ventricular septum revealed the diffuse deposition of ATTR (Figure 2A–2C) with little fibrosis confirmed by Picosirius Red staining (Figure 2D).

When non-invasively estimated using MRI-derived LV volumes and echo-derived end-diastolic pressure,^{1,2} the

end-diastolic pressure–volume relation significantly shifted upward and leftward towards decreased distensibility during the previous 5 years (Figure 3A). Invasive LV pressure–volume curves during inferior vena cava occlusion demonstrated increase of both effective arterial elastance of 3.6 mmHg/mL and LV end-systolic elastance of 5.4 mmHg/mL. Although the resting left ventricular end-diastolic pressure (LVEDP) was within the normal range (7 mmHg), the LV stiffness constant calculated from the slope of the end-diastolic pressure–volume relation^{3,4} was 0.050, suggesting a stiff LV. A prolonged time constant of LV relaxation of 90 ms was also observed.⁵ As genetic testing confirmed Val30Met mutation, she was diagnosed with late-onset hereditary ATTR with cardiomyopathy and polyneuropathy. Tafamidis meglumine was initiated.

Discussion

To our knowledge, this is the first report of the LV function and morphology using pressure–volume analysis in a

Figure 2 Histology on (A) haematoxylin–eosin staining, (B) direct fast scarlet staining, (C) immunostains for transthyretin amyloid, and (D) Picosirius Red staining.

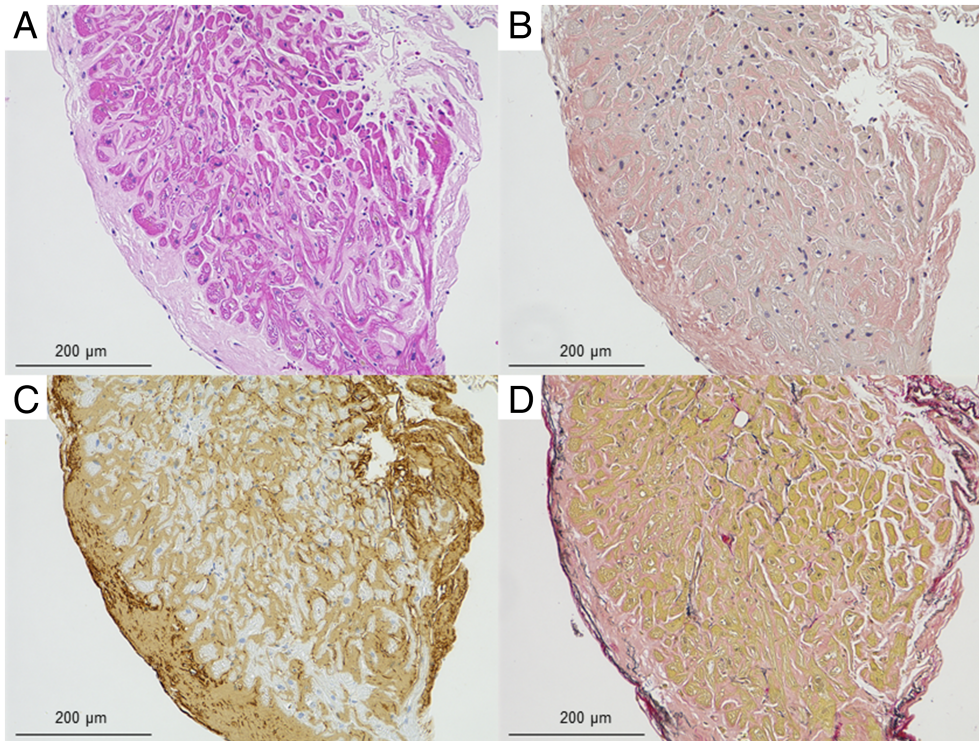
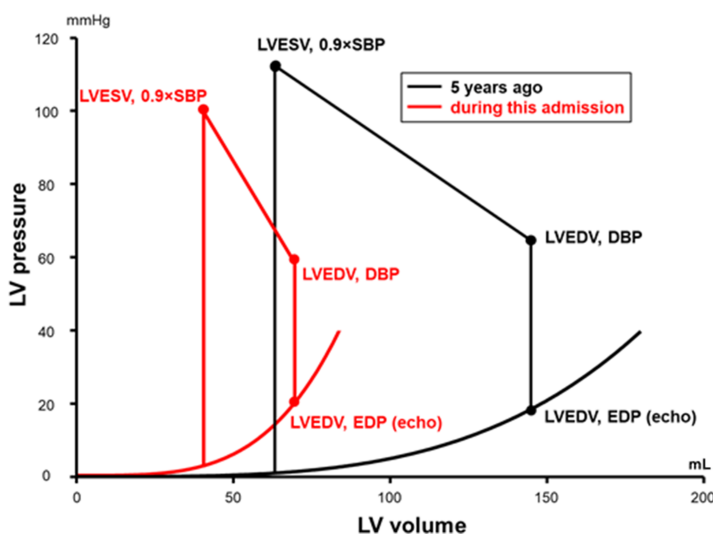
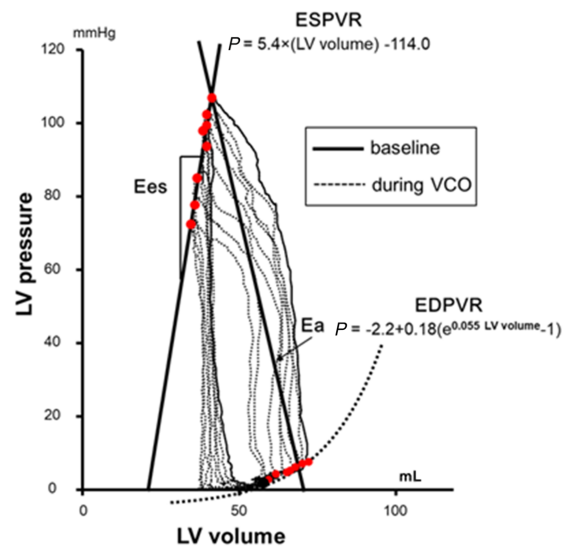


Figure 3 (A) Non-invasive pressure–volume (PV) relationships estimated from the brachial systolic (SBP) and diastolic blood pressures (DBP), cardiac magnetic resonance imaging-derived left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes, and Doppler-derived left ventricular end-diastolic pressure (LVEDP). The LV end-systolic pressure was estimated to be $0.9 \times \text{SBP}$. The LVEDP was estimated by $11.96 + 0.596 \times (E/e')$. Single-beat EDPVR was estimated as $P = \alpha \cdot V^\beta$. (B) Invasive LV PV curves during inferior vena cava occlusion (IVCO), including end-systolic elastance (Ees: 5.4 mmHg/mL) calculated from the slope of end-systolic PV relationship (ESPVR), effective arterial elastance (Ea: 3.6 mmHg/mL), and end-diastolic PV relationship (EDPVR). The EDPVR was described by $P = P_0 + \alpha (e^{\beta V} - 1)$, where P is LV pressure, P_0 is pressure offset, α is the curve fitting constant, V is LV volume, and β is the chamber stiffness constant.

A Changes in non-invasive PV curves



B Invasive PV curves during IVCO



Val30Met patient at different time points. Significant morphological alterations, such as the progression of concentric LV hypertrophy and the decrease in LV cavity size, were observed during a 5 year period in our patient. In addition, prolonged LV relaxation, LV stiffening similar to that in heart failure with preserved ejection fraction patients in our hospital,⁴ and alterations in ventricular–vascular coupling were observed during this admission. Right ventricular apical pacing may negatively affect LV systolic function and reduce the stroke volume with a larger LV end-diastolic volume. However, the LV end-diastolic volume was smaller and the LV ejection fraction was maintained in our patient. Thus, the observed functional and morphological changes in the LV could have been related to the disease progression over time, as non-invasively suggested by cardiac ATTR.⁶ In addition, the significant decrease in physical activity due to progressive peripheral muscular atrophy over time may have been related to stiffening of the LV and a decrease in distensibility, as observed in previously healthy but sedentary subjects after prolonged bed rest.⁷ Although she had normal LVEDP and BNP, she had dyspnoea on effort and dilated left atrium. Heart failure with preserved ejection fraction patients with normal BNP and LV filling pressure could have abnormally elevated LV filling pressures during exercise at low intensity.⁸ We speculate that her dyspnoea on effort could be related to the elevated LV filling pressure, especially during exertion.

Although we observed LV stiffening and concentric LV remodelling, the LV wall was not thickened on admission. There are a few treatment options for patients with hereditary ATTR cardiomyopathy. For example, inotersen improves polyneuropathy and may have a potential to prevent further LV thickening.⁹ As inotersen has not been permitted for use in Japan, tafamidis was initiated in our

patient. We speculate that the LV wall would be more thickened if the treatment for amyloid was not initiated. By using pressure–volume curves, the treatment effects on LV stiffness, LV systolic function, and ventricular–vascular coupling can be assessed in patients with ATTR cardiomyopathy. To evaluate the treatment effects on LV stiffness, the use of invasively measured LVEDP might be better as tissue Doppler-derived index of LV filling pressure might not accurately estimate LVEDP in cardiac amyloidosis.

Magnetic resonance imaging with LGE is a reliable method for assessing cardiac amyloidosis with a high sensitivity and specificity, especially in cardiac ATTR.¹⁰ However, the early diagnosis of ATTR cardiomyopathy could have been difficult in such patients with neither LGE nor relative apical sparing pattern of longitudinal strain. Our patient with the Val30Met transthyretin mutation had conduction disturbance, such as left anterior fascicular block and first-degree AV block, when she developed silent MI 5 years ago. This suggested that she had amyloid deposition in the myocardium to a certain degree, although cardiac MRI demonstrated no LGE in the LV wall. Follow-up cardiac MRI with global native T1 and extracellular volume and/or 99mTc-pyrophosphate scintigraphy may be required in patients who exhibit gradual deterioration of LV diastolic and systolic functions, and clinical findings, such as carpal tunnel syndrome and peripheral neuropathy, even if no LGE was observed on previous cardiac MRI.

Conflict of interest

None declared.

References

1. Klotz S, Hay I, Dickstein M, Yi GH, Wang J, Maurer M, Kass D, Burkhoff D. Single-beat estimation of end-diastolic pressure–volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* 2006; **291**: 403–412.
2. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular–vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation* 2007; **115**: 1982–1990.
3. Kawaguchi M, Hay I, Fetis B, Kass D. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003; **107**: 714–720.
4. Omori T, Nakamori S, Fujimoto N, Ishida M, Kitagawa K, Ichikawa Y, Kumagai N, Kurita T, Imanaka-Yoshida K, Hiroe M, Sakuma H, Ito M, Dohi K. Myocardial native T1 predicts load-independent left ventricular chamber stiffness in patients with HFpEF. *JACC Cardiovasc Imaging* 2020; **13**: 2117–2128.
5. Raff G, Glantz S. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog heart. *Circ Res* 1981; **24**: 813.
6. Bhuiyan T, Helmke S, Patel AR, Ruberg FL, Packman J, Cheung K, Grogan D, Maurer MS. Pressure–volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122i mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail* 2011; **4**: 121–128.
7. Hastings JL, Krainski F, Snell PG, Pacini EL, Jain M, Bhella PS, Shibata S, Fu Q, Palmer MD, Levine BD. Effect of rowing ergometry and oral volume loading on cardiovascular structure and function during bed rest. *J Appl Physiol* 2012; **112**: 1735–1743.
8. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; **3**: 588–595.
9. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH 3rd, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceição I, Schmidt HH, Vita G,

Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen treatment for patients with hereditary

transthyretin amyloidosis. *New Engl J Med* 2018; **379**: 22–31.

10. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, Rosmini S, Quarta CC, Whelan

CJ, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Magnetic resonance in transthyretin cardiac amyloidosis. *J Am Coll Cardiol* 2017; **70**: 466–477.