Therapeutic Strategy for Heart Failure with Reduced Ejection Fraction and Cardiac Amyloidosis

Teruhiko Imamura, MD, Toshihide Izumida, MD, Makiko Nakamura, MD and Koichiro Kinugawa, MD

Summary

We sometimes encounter patients with systolic heart failure and cardiac amyloidosis. Neurohormonal blockers are guideline-directed medical therapy for those with systolic heart failure. However, its implication among the above cohort remains controversial. Of 3 patients with systolic heart failure and cardiac amyloidosis who we encountered, cardiac reverse remodeling was achieved in 2 patients who received neurohormonal blockers, whereas cardiac function remained unchanged in a patient not receiving neurohormonal blockers. Neurohormonal blockers might be keys to achieve cardiac reverse remodeling and favorable clinical outcomes even in patients with systolic heart failure and cardiac amyloidosis, although further larger-scale studies are required to validate our hypothesis.

Key words: Tafamidis, Hemodynamics

Cardiac amyloidosis is one of the subtypes of systemic wild-type ATTR amyloidosis, which causes end-organ dysfunction via the deposition of amyloid in various organs.1 Cardiac amyloidosis, in general, presents as heart failure with preserved ejection fraction (HFpEF) accompanying diastolic dysfunction. Similar to other HFpEF diseases, neurohormonal blockers are considered to be refractory.2 Diuretics are administered in an attempt to relieve the congestive symptoms.

However, we sometimes encounter patients with cardiac amyloidosis accompanying heart failure with reduced ejection fraction (HFrEF). Neurohormonal blocker administration is a guideline-directed medical therapy for those with HFrEF,2 whereas its clinical implication in those with HFpEF and cardiac amyloidosis remains controversial.

We had 3 patients who had HFrEF due to cardiac amyloidosis, 2 of whom received neurohormonal blockers and achieved cardiac reverse remodeling. We will discuss the potential of neurohormonal blockers on those with HFrEF and cardiac amyloidosis.

Case Report

Case 1 (no neurohormonal blocker): An 85-year-old man was admitted to our institute complaining of dyspnea in August 2019. His left ventricular end-diastolic diameter (LVDd) was 44 mm and the left ventricular ejection fraction (LVEF) was 48% (Figure A). He had left ventricular hypertrophy despite no history of hypertension. He was diagnosed with wild-type ATTR cardiac amyloidosis. His symptom was improved by 30 mg of azosemide and he was discharged. No other anti-heart failure medications were attempted.

One year later, his LVDd was 48 mm and the LVEF had decreased to 35%. The New York Heart Association functional class was III. Tafamidis, which binds to transthyretin and prevents tetramer dissociation and amyloidogenesis, was initiated. Six months later, his LVDd was 51 mm and his LVEF remained at 35% with persistent left ventricular hypertrophy.

Case 2 (on neurohormonal blocker): An 83-year-old man was admitted to our institute complaining of dyspnea with New York Heart Association functional class II in October 2016. His LVDd was 48 mm and the LVEF was 25% (Figure B). The interventricular septum and posterior wall thickness were 16/15 mm. He was diagnosed with wild-type ATTR cardiac amyloidosis. Spirolactone 50 mg/day and enalapril 1.25 mg/day were initiated. Beta-blocker administration was not attempted due to his relatively low heart rate: 64 bpm.

Three-month follow-up echocardiography showed an LVDd of 47 mm and improvement in the LVEF to 30%. The interventricular septum and posterior wall thickness were 16/15 mm. He was diagnosed with wild-type ATTR cardiac amyloidosis. Spirolactone 50 mg/day and enalapril 1.25 mg/day were initiated. Beta-blocker administration was not attempted due to his relatively low heart rate: 64 bpm.

Case 3 (on neurohormonal blocker): A 70-year-old man was diagnosed with wild-type ATTR cardiac amyloidosis in December 2020. Tafamidis was initiated in April 2021. Nevertheless, he was admitted to our institute again complaining of dyspnea with New York Heart Association functional class II in September 2021. His LVDd was 48 mm and the LVEF was 30%.

Three-month follow-up echocardiography showed an LVDd of 47 mm and improvement in the LVEF to 30%. The interventricular septum and posterior wall thickness had decreased slightly to 13/11 mm.

Case 2 (on neurohormonal blocker): An 83-year-old man was admitted to our institute complaining of dyspnea with New York Heart Association functional class II in October 2016. His LVDd was 48 mm and the LVEF was 25% (Figure B). The interventricular septum and posterior wall thickness were 16/15 mm. He was diagnosed with wild-type ATTR cardiac amyloidosis. Spirolactone 50 mg/day and enalapril 1.25 mg/day were initiated. Beta-blocker administration was not attempted due to his relatively low heart rate: 64 bpm.

Three-month follow-up echocardiography showed an LVDd of 47 mm and improvement in the LVEF to 30%. The interventricular septum and posterior wall thickness had decreased slightly to 13/11 mm.

Case 3 (on neurohormonal blocker): A 70-year-old man was diagnosed with wild-type ATTR cardiac amyloidosis in December 2020. Tafamidis was initiated in April 2021. Nevertheless, he was admitted to our institute again complaining of dyspnea with New York Heart Association functional class II in September 2021. His LVDd was 48 mm and the LVEF was 30%.

Three-month follow-up echocardiography showed an LVDd of 47 mm and improvement in the LVEF to 30%. The interventricular septum and posterior wall thickness had decreased slightly to 13/11 mm.

From the Second Department of Internal Medicine, University of Toyama, Toyama, Japan.
Address for correspondence: Teruhiko Imamura, MD, The Second Department of Internal Medicine, University of Toyama, 2630 Sugitani, Toyama, Toyama 930-0194, Japan. E-mail: teimamu@med.u-toyama.ac.jp
Received for publication October 1, 2021. Revised and accepted December 20, 2021.
doi: 10.1536/ihj.21-664
All rights reserved by the International Heart Journal Association.
functional class III. His LVDd was 50 mm, the LVEF was 39%, and the inter-ventricular septum and posterior wall were 14/13 mm (Figure C).

Carvedilol 2.5 mg/day, enalapril 2.5 mg/day, spironolactone 25 mg/day, as well as dapagliflozin 10 mg/day were initiated. Due to the electrocardiogram features (complete left bundle branch block and QRS duration 148 msec), cardiac resynchronization therapy with a defibrillator was initiated. Adaptive servo-ventilation was also initiated due to the remaining congestion.

Three months later, his LVDd was 48 mm, the LVEF was 48%, and the inter-ventricular septum and posterior wall thickness were 13/12 mm. The New York Heart Association functional class improved to II.

Discussion

Tafamidis and cardiac reverse remodeling: Tafamidis suppresses further deposition of amyloid in the myocardium and delays the disease progression. The ATTRACT trial observed remaining intraventricular thickness during the 30-month tafamidis treatment. In our cases, 2 out of 3 patients received tafamidis. The case 2 patient did not receive tafamidis because it had not yet been indicated for those with cardiac amyloidosis at that time. In case 1, cardiac size and function remained unchanged or rather progressed following the initiation of tafamidis. In case 3, heart failure developed despite the tafamidis therapy. The New York Heart Association functional class was III in both cases. Tafamidis administration should be initiated at an earlier stage (functional class I or II) to achieve clinical efficacy. Given its cost-effectiveness, tafamidis should perhaps not be recommended for those with functional class III or IV. Again, given its mechanism, cardiac reverse remodeling would not be expected by the tafamidis therapy alone even though it is initiated at an earlier stage.

Neurohormonal blockers and cardiac reverse remodeling: The implication of neurohormonal blockers in patients with HFrEF and cardiac amyloidosis remains controversial and there is no established therapeutic consensus thus far. Therapeutic strategies including medication are at the discretion of the attending cardiologists at our institute. Case 1 did not receive these medications whereas case 2 and case 3 did receive them. Reverse remodeling was not achieved in case 1 whereas 5-10% LVEF improvement was achieved in cases 2 and 3.

Based on these findings, neurohormonal blockers might be associated with cardiac reverse remodeling, although its impact on secondary cardiomyopathy like amyloidosis would be partially due to underlying myocardial disorder. Since the greatest improvement in LVEF was observed in case 3, tafamidis-incorporated neurohormonal blocker therapy, instead of neurohormonal blocker alone, might be recommended. Furthermore, case 3 received non-pharmacological therapies including cardiac resynchronization therapy and adaptive servo-ventilation therapy, both of which are in general considered for those with HFrEF. The great improvement in cardiac function could be explained by such a multidisciplinary therapy. Further studies are warranted to validate our hypothesis. A multi-center study is needed given the rarity of this disease.

Several recent studies have reported that neurohormonal blockers were safe in patients with cardiac amyloidosis. Nevertheless, unintended hypotension might be triggered by up-titration of these medications due to the nature of potential diastolic dysfunction. An appropriate heart rate also remains unknown. A heart rate of approximately 50-60 bpm is considered to be ideal for those with HFrEF, whereas a relatively higher heart rate seems to be more suitable for those with diastolic dysfunction. In case 2, we hesitated to use beta-blockers because of his relatively lower heart rate. We did not perform cardiac...
magnetic resonance imaging. Such a modality might be useful for predicting the potential of reverse remodeling beforehand.

**Disclosure**

**Conflicts of interest:** None.

**References**


