

Reverse Remodeling and Genetics: A Review Based on a Clinical Case Description that Challenges Current Evidence and Logic

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Abstract

Cardiac remodeling, present in heart failure (HF), is a compensatory biological process following an initial myocardial injury that gradually becomes maladaptive, leading to clinical deterioration and chronic HF.

Reverse remodeling (RR), which has been increasingly addressed, occurs when the geometry and/or function of the left ventricle recover in response to treatment, approaching normal cardiac structure. RR is associated with a better prognosis.

Factors associated with RR include female sex, non-ischemic etiology, mild to moderate HF, lower fibrotic burden, elevated blood pressure permitting medical optimization, shorter disease duration, and preserved renal function. However, growing knowledge of genetic factors in HF etiology has provided important insights into their role in treatment response and prognosis.

To illustrate and discuss these emerging topics, we report a case of advanced HF involving RR and a genetic variant, reviewing current recommendations for management.

Introduction

Cardiac remodeling is an adaptive, compensatory biological process, defined as any change in the geometry and function of the cardiac chamber, which may occur in response to an initial myocardial insult with sustained physiological or pathophysiological stimuli, such as cardiac injury, hemodynamic changes, and inflammation or neurohormonal activation. Gradually, cardiac remodeling becomes maladaptive, causing clinical deterioration and chronic heart failure (HF).^{1,2}

Guideline-recommended pharmacological treatment aims to interrupt this deleterious chain caused by the initial event, with the purpose of clinical improvement and patient survival, and may occasionally result in recovery of ventricular function.

Keywords

Heart Failure; Heart Transplantation; Reverse Remodeling; Dilated Cardiomyopathy; Genetics

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For many years, HF was treated as an incurable and immutable chronic disease. However, years of observation and studies provided evidence that both outcomes and ventricular function could improve, prompting the European guideline to introduce the term “heart failure with recovered ejection fraction” in 2021.³

Studies of explants from heart transplant recipients after a period of mechanical circulatory support with left ventricular assist devices showed, for the first time, that the end-diastolic pressure-to-volume ratio of end-stage human hearts can substantially return to normal values. However, it is still unclear whether this reversal of the remodeling process truly represents restoration of detailed aspects of cardiac chamber structure, as well as permanent chemical and cellular normalization.⁴

Still defined as a chronic disease, HF is currently recognized as a dynamic and recoverable condition. To this end, the Brazilian, American, and European guidelines have recommended early optimization of pharmacological treatment, as reinforced by Mebazaa et al. in the STRONG-HF study.^{3,5-7}

In parallel, growing knowledge has highlighted the genetic substrate of HF. The influence of the genetic substrate on response to standard HF treatment, reverse remodeling (RR), and clinical management recommendations represents an important field for further research and new evidence.

Case Report

We report the case of a 48-year-old male patient with no known prior comorbidities. He was admitted to the emergency room on June 1, 2024, complaining of dyspnea on minimal exertion for 4 days, paroxysmal nocturnal dyspnea, and malaise. He denied chest pain and syncope. During anamnesis, he reported a mild viral respiratory infection approximately 4 weeks prior, without other memorable symptoms. He had a history of active smoking with a smoking load of approximately 10 pack-years, denied alcoholism or use of other drugs, and was sedentary.

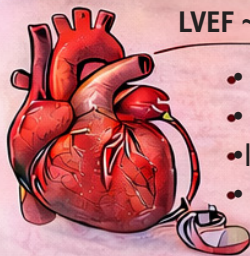
Physical examination revealed a heart rate of 58 bpm, blood pressure of 137/100 mmHg, oxygen saturation of 95%, signs of congestion characterized by jugular vein distension and hepatojugular reflux, and bibasilar crackles. Electrocardiogram (ECG) showed sinus rhythm, signs of left ventricular hypertrophy, and slow R wave progression in precordial leads (V1 to V3). Laboratory test results included NT-proBNP 13,000 pg/mL and creatinine 1.38 mg/dL.

Central Illustration: Reverse Remodeling and Genetics: A Review Based on a Clinical Case Description that Challenges Current Evidence and Logic



ABC Heart Failure & Cardiomyopathy

Initial Injury & Unfavorable Predictors



LVEF ~8%

BB

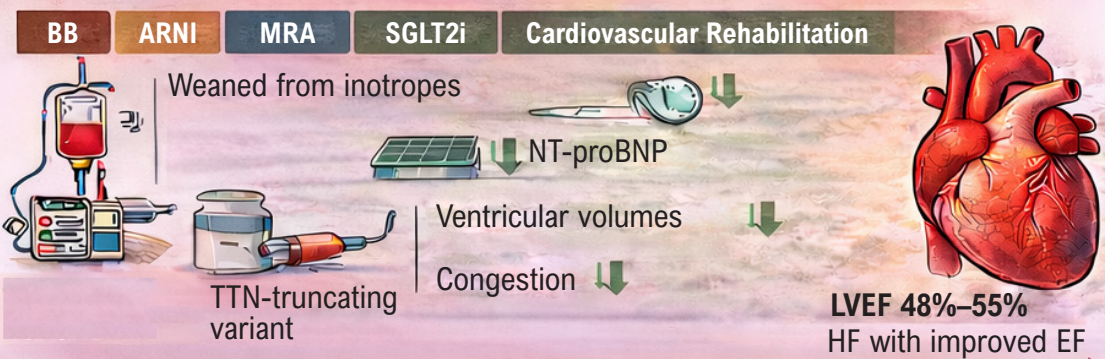
ARB

MRA

- Advanced HFrEF
- Non-ischemic DCM
- INTERMACS 3
- Listed for transplant
- Continuous IV inotropes

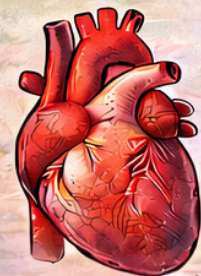
Mid-wall fibrosis
Diameter (80 mm)

Reverse Remodeling + Guideline-Directed Therapy + Time



Complete Reverse Remodeling

- ✓ HF with improved EF
- ✓ Transplant delisted
- ✓ Ventricular function normalized
- ✓ Fibrosis absent



GENETICS × PHENOTYPE × THERAPY

Genotype does not dictate destiny – response is dynamic and modifiable.

ABC Heart Fail Cardiomyop. 2025; 5(4):e20250026

Reverse remodeling and genetics. ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; BB: beta-blocker; DCM: dilated cardiomyopathy; EF: ejection fraction; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium–glucose cotransporter 2 inhibitors.

Review Article

Management for acute HF was initiated in the emergency room, with a satisfactory response to diuretics, and concomitant etiological investigation was performed. Transthoracic echocardiography (TTE) showed biventricular dysfunction with thrombus in the left ventricle (LV), enlarged left chambers, eccentric hypertrophy, and diffuse hypokinesia that was predominant in the apical and inferior wall of the LV. The patient was started on dapagliflozin 10 mg/day, sacubitril/valsartan 50 mg every 12 hours (which was not tolerated due to hypotension), and spironolactone 25 mg.

The patient was admitted to the coronary care unit, with continued diuretic therapy, non-invasive positive pressure ventilation, and the need for low-flow nasal oxygen. Due to signs of low cardiac output, dobutamine 2.5 mcg/kg/min was started, with dose titration. On the second day of hospitalization, the patient developed atrial fibrillation with rapid ventricular response, controlled with amiodarone (intravenous loading dose of 150 mg, followed by continuous infusion of 900 mg/24 hours), achieving rate and rhythm control.

Regarding etiological investigation, coronary computed tomography angiography was initially scheduled. However, due to high heart rate, cardiac catheterization was chosen, which did not show significant obstructive coronary lesions. Cardiac magnetic resonance imaging (CMR) showed late mid-wall enhancement in the septal, inferior, and mid-basal lateral segments, consistent with non-ischemic myocardial fibrosis, absence of edema, no abnormalities on tissue mapping, left ventricular ejection fraction (LVEF) of 8%, and a fractional area change of 19%. CMR also revealed a thrombus measuring $1.5 \times 1.2 \times 0.5$ cm adhering to the medial anteroseptal segment of the LV (Figure 1).

The etiological diagnosis was defined as dilated cardiomyopathy (DCM). During hospitalization, the patient's condition progressed; he became dependent on inotropic agents and experienced 3 failed weaning attempts. He was listed for heart transplantation, remaining in INTERMACS 3 on metoprolol succinate 50 mg every 12 hours, losartan 50 mg every 12 hours, spironolactone 25 mg, furosemide (with transition from intravenous to oral form), and dobutamine 7.5 mcg/kg/min.

His clinical progression was favorable, without secondary organ dysfunction, undergoing daily physiotherapy and cardiac rehabilitation twice a week.

A progressive reduction in cardiac area was observed on chest radiography (Figure 2). Repeat TTE was performed 3 months later, while still on dobutamine 7.5 mcg/kg/min, with LV diameters of 56×46 mm and LVEF of 38%. Medications for HF were optimized to maximum tolerance, and complete weaning from dobutamine occurred after 90 days of hospitalization.

A new TTE, 1 month later, off inotropic support, showed LV diastolic diameter of 59 mm and LVEF of 27%. The patient was asymptomatic and clinically stable, achieving 105% of predicted 6-minute walk test distance. He was discharged from the hospital on October 15, 2024, using metoprolol succinate 50 mg every 12 hours, dapagliflozin 10 mg, spironolactone 25 mg, captopril 25 mg every 8 hours, atorvastatin 20 mg, lipidil 160 mg, and warfarin 2.5 mg 5 times a week.

The patient returned for an outpatient consultation 15 days later, and captopril was switched to sacubitril/valsartan after a washout. The patient continues with cardiac rehabilitation twice a week, in New York Heart Association functional class I, without complications. The patient was using metoprolol succinate 50 mg every 12 hours, sacubitril/valsartan 100 mg every 12 hours

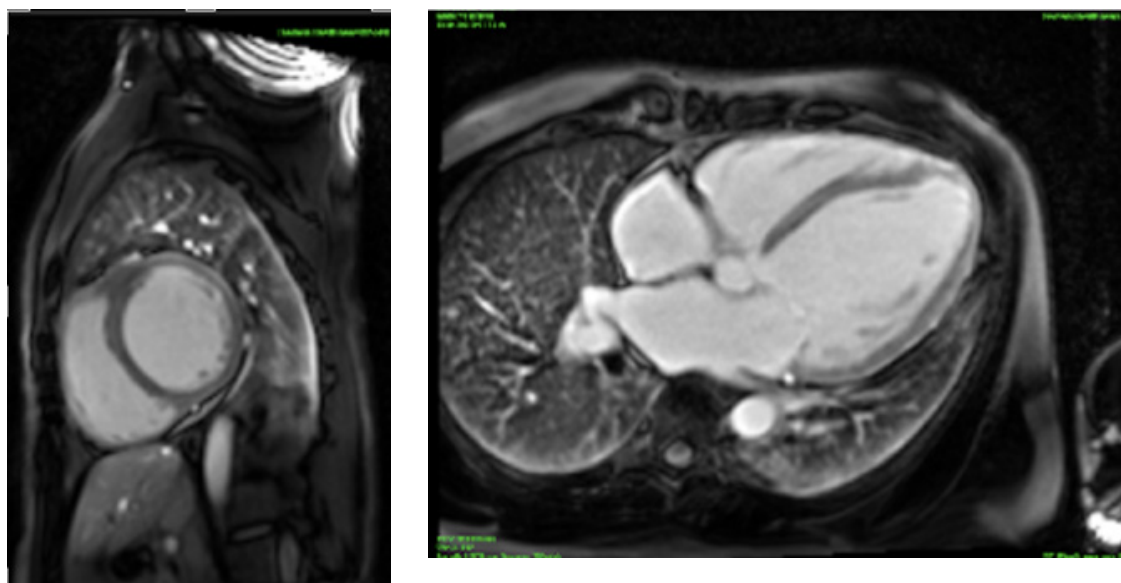


Figure 1 – Cardiac magnetic resonance imaging showing late mid-wall enhancement in the septal, inferior, and mid-basal lateral segments, consistent with non-ischemic myocardial fibrosis. Source: Patient data.

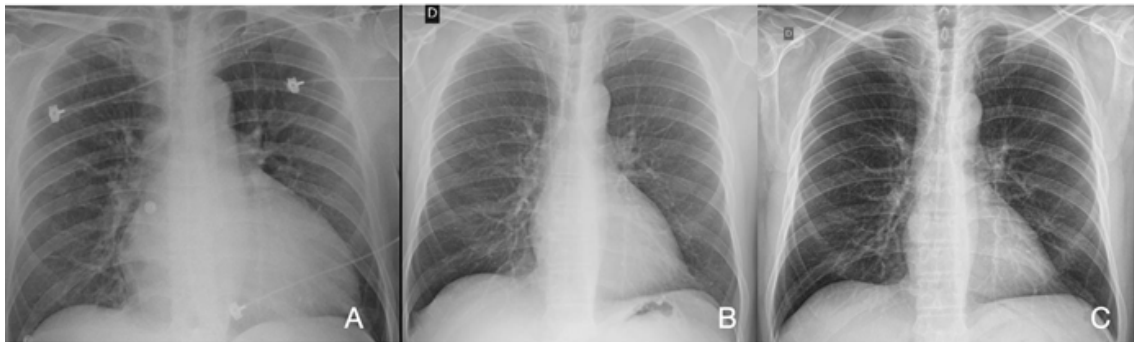


Figure 2 – Serial chest X-ray findings. A: Admission (June 1, 2024); B: During hospitalization, on dobutamine (September 4, 2025); C: Outpatient follow-up (February 12, 2025). Source: Patient data.

(started on an outpatient basis in October 2024), spironolactone 25 mg/day, and dapagliflozin 10 mg/day. CMR, performed on November 18, 2025, showed normal chamber sizes, LVEF of 48%, and no evidence of edema, fibrosis, or LV thrombus (Figure 3). The anticoagulant was discontinued, and the patient was delisted from the transplant waiting list.

The last TTE performed in May 2025 showed fully recovered biventricular function and normal chamber diameters. Table 1 displays the patient's echocardiographic progress.

During etiological investigation, a genetic panel was collected for DCM, showing a variant in the *TTN* gene, NM_133378.4:c.98465C>Gip.(Ser32822*), classified as probably pathogenic by the American College of Medical Genetics. Genetic counseling and family screening were performed.

Definition

Recognizing that LVEF can improve substantially in a subgroup of patients with heart failure with reduced ejection fraction (HFrEF) treated with medical therapies or devices has led to intense interest in their outcomes and clinical management, as well as in understanding how these patients differ from those with more modest responses or little impact on LVEF (non-responders).⁴

Ventricular remodeling, although initially compensatory, is related to the progression of cardiac dysfunction if left untreated. RR, with normalization of geometry and function, is associated with better prognosis and can be considered a surrogate endpoint in clinical studies.⁸ Imaging tools, circulating biomarkers (NT-proBNP and high-sensitivity troponin), and clinical criteria should be integrated into HF monitoring, aiming for early and personalized intervention.²

The definition of RR, however, is not yet uniform. Terms such as HF with “recovered” or “improved” ejection fraction (EF) are used, but there is no consensus on the minimum EF increase required.^{8,9} The 2021 international consensus (AHA/ESC/JHFS) proposed the term “HF with improved EF” for patients with baseline EF $\leq$ 40%, an increase $\geq$ 10 percentage points, and a subsequent EF $>$ 40%.¹⁰ A similar definition was published by JACC in 2020, including the distinction between partial recovery

(EF 40% to 50%) and complete recovery ($>$ 50%).⁸ The 2022 ACC/AHA guideline adopts only initial EF $\leq$ 40% and final EF $>$ 40%, whereas the 2021 European guideline uses final EF $\geq$ 50%, without establishing a minimum interval between examinations.^{3,10}

The prevalence of RR is related to the etiology of cardiomyopathy and the diagnostic criteria adopted.² In HFrEF studies, it varies between 26% and 46%.¹¹ Metabolic, toxic, and inflammatory insults are among the main triggers, especially tachycardia-induced cardiomyopathy, takotsubo syndrome, and thyrotoxicosis, in which complete recovery may reach 60% to 100% of cases.¹⁰

Relevant RR rates have also been observed in peripartum cardiomyopathy and acute lymphocytic myocarditis. Another favorable scenario for RR is when cardiotoxic agents, such as alcohol and certain chemotherapeutic agents (anthracyclines, tyrosine kinase inhibitors, and monoclonal antibodies), are discontinued.²

Predictors

LVEF generally increases in response to medical treatment and, in some cases, to device therapy, according to established guidelines.¹

Although studies use varying definitions of RR, the following factors consistently appear as predictors associated with greater likelihood of LVEF recovery: non-ischemic etiology, shorter duration of HF, absence of late gadolinium enhancement on CMR, lower degree of initial remodeling, female sex, elevated blood pressure permitting medical optimization, preserved renal function, and reduced BNP levels during pharmacological therapy.^{12,13}

The Heart Failure Optimization Study (HF-OPT), conducted with patients with HFrEF and LVEF $\leq$ 35% between 2017 and 2022, showed that 68% experienced functional recovery in less than 6 months, and 77% achieved LVEF $>$ 35% within 1 year. The use of recommended therapies was high: 97% with beta-blockers, 94% with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors, and 62% with mineralocorticoid antagonists. However,

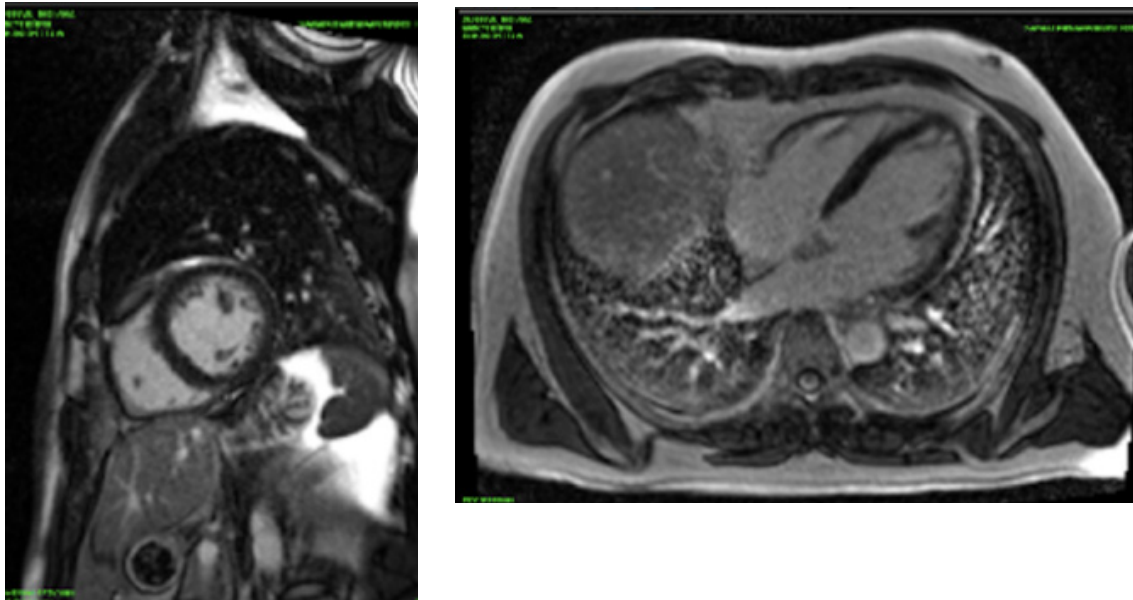


Figure 3 – Cardiac magnetic resonance imaging showing normal-sized chambers and absence of fibrosis. Source: Patient data.

Table 1 – Serial echocardiography findings during patient treatment and follow-up

	Echocardiography findings						
	June 2024	September 9, 2024 (with dobutamine 7.5 mcg/kg/min)	September 23, 2024 (with dobutamine 5 mcg/kg/min)	September 24, 2024	October 2, 2024	February 2025	May 2025
LVEF (%)	18	38	39	37	27	43	59
RV function	Preserved	Mild dysfunction	Preserved	Preserved	Preserved	Preserved	Preserved
LVEDD (mm)	71	56	56	57	59	55	46
LA (mm)	46	42	38	36	37	35	34
LAVi (mL/m ²)	43	39	27.6	26.3	27	31.8	26
LVMI (g/m ²)	166	121.1	104.6	116	98.4	94.6	74.6
MR	Mild	Minimal	Minimal	Minimal	Minimal	Minimal	Minimal

LA: left atrial diameter; LAVi: left atrial volume indexed by body surface area; LVEDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MR: mitral regurgitation; RV: right ventricle. Source: Patient data.

only 9% achieved the target dose for all three classes, which was significantly associated with improved LVEF ($p = 0.048$).¹⁴

Genetics

Clinical assessment identifies 30% to 50% of patients with DCM as having an affected or likely affected relative, implying a genetic cause. Nonetheless, pathogenic or likely pathogenic variants have been found in only 20% to 30% of cases.¹⁵

A complete 3-generation family history is always recommended for patients with non-ischemic DCM, regardless of LVEF or clinical trajectory, as there are implications for the patient’s prognosis

and recovery, as well as for descendants and other first-degree relatives. It is advisable for physicians to apply a low threshold for performing genetic testing, even among those with recovered DCM, because the results can provide information on prognosis, recovery durability, risk of HF recurrence or sudden death, atrial arrhythmias, and familial HF risk.⁸

Prognosis in genetic DCM varies according to the genetic group affected. Truncating variants in the titin gene (*TTN*tv) are more likely to respond favorably to guideline-directed medical therapy and achieve heart failure with improved ejection fraction (HFIEF), whereas mutations in the *LMNA* gene are less likely to respond and confer a high risk of sudden death.⁸

In 2012, Herman et al. reported that 15% to 25% of DCM cases were associated with rare *TTN*ts. Titin is the largest protein in the heart, spanning the entire length of the sarcomere, from the Z-disc to the M-band, and it functions as a molecular spring that regulates contraction.¹⁶

In contrast to other known genetic etiologies of DCM, *TTN*ts have been associated with recovery after exposure to optimized medical treatment and left ventricular assist device decompression; however, it is worth emphasizing that the sustainability of these improvements has not been completely characterized.⁸

Prognosis

Although RR is generally associated with favorable prognosis, it is not considered a cure, and patients remain at risk of relapse. Therefore, some authors have adopted terms such as remission and myocardial recovery to differentiate cases where the insult is permanent, with a risk of decreased LVEF, from cases where sustained recovery is expected.¹⁶

Clinical assessment of symptoms and ECG can identify patients with HFIEF at higher risk of relapse, patients who require persistent diuretic therapy, and those with left bundle branch block, representing higher-risk subgroups.^{17,18} The absence of late gadolinium enhancement on CMR is a strong predictor of recovery and is associated with a better prognosis. Elevated extracellular volume values (suggestive of edema or fibrosis) can also improve the diagnostic assessment of specific cardiomyopathies.¹⁹⁻²⁴ Higher absolute global longitudinal strain values (e.g., > 16%) have been associated with stable LVEF in short-term follow-up, and even among dilated hearts, higher global longitudinal strain has been associated with achieving HFIEF status.^{25,26}

In the case reported, the initial CMR showed mid-wall late enhancement in the septal, inferior, and mid-basal lateral segments, which represents a negative predictor of RR; nonetheless, the patient's genetic factors combined with optimized medical therapy may have prevailed. CMR after remodeling, showing recovered LVEF and absence of fibrosis, confirmed the clinical improvement. However, the reversal of late enhancement is not the typical behavior of true myocardial scarring, and this observation suggests that the substrate could be predominantly inflammatory or functional, rather than necessarily fibrotic. Furthermore, it highlights an important area of uncertainty in the prognostic interpretation of fibrosis, since its presence and subsequent disappearance challenge the traditional notion that late enhancement always represents irreversible damage.

Ultimately, this finding emphasizes that late enhancement should be interpreted in the clinical, temporal, and therapeutic context and that myocardial tissue may, in certain scenarios, have a greater capacity for recovery than previously supposed.

A recent Brazilian study identified predictors of long-term RR maintenance, both clinical (fewer symptoms, higher systolic blood pressure, and non-use of furosemide) and echocardiographic (greater LVEF gain, greater reduction in left ventricular systolic diameter, and larger septum), which may contribute to understanding and managing this situation. However, few cohorts have addressed genetic assessment as a predictor in RR maintenance.²⁶

Greater reductions in NT-proBNP with neurohormonal therapy for HF are associated with improvements in LV structure and function, as well as better clinical outcomes. An increase in NT-proBNP in patients with HFrEF may precede HF relapse. There are still gaps in early cohort studies aimed at better understanding the natural history of HFrEF, and additional clinical trials are needed to define which clinical treatment elements are important to maintain clinical remission, as well as basic studies to better define its biology in order to develop new therapeutic targets.

Conclusion

Over the past two decades, we have made significant progress in understanding the biology, epidemiology, clinical predictors, and outcomes associated with RR in HF. However, knowledge about the natural history and long-term outcomes of patients with HFIEF remains limited, particularly considering the genetic component and the wide phenotypic heterogeneity involved.

The case reported in this manuscript strikingly demonstrates how clinical behavior can diverge from trajectories predicted in the literature. This dissociation between genotype and phenotype, although rare, broadens the discussion regarding the influence of genetic variants on therapeutic response, stimulating critical reflection on our approaches to risk stratification, follow-up, and interpretation of treatment responses.

Future research will be strengthened by more refined phenotyping of patients, deepened genomic studies, and improved understanding of the mechanisms that modulate structural recovery. Advances in this direction will allow us not only to better understand the natural history of HFIEF, but also to identify which components of treatment are essential to induce and maintain clinical remission and to define subgroups of patients with the potential for unexpected recovery.

In summary, the reported case illustrates the increasing complexity of contemporary cardiomyopathy management, challenges established paradigms, and demonstrates the extent to which we still need to evolve in order to integrate genetics, phenotype, and therapeutic response accurately in clinical practice.

Author Contributions

Conception and design of the research: Betinardi HG; Acquisition of data: Betinardi HG, Hames RL, Koroishi JHY; Analysis and interpretation of the data: Betinardi HG, Furquim S, Koroishi JHY; Statistical analysis: Hames RL; Writing of the manuscript: Betinardi HG, Furquim S; Critical revision of the manuscript for intellectual content: Bernardi HGB, Furquim S, Koroishi JHY, Pinheiro Junior JA, Martins SK.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Review Article

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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