

A Case of Low Ejection Fraction Unrelated to Anthracycline Therapy: Chemo Tells a Fib

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Received March 7, 2023; Accepted for publication May 16, 2023; Published online July 25, 2023
<https://doi.org/10.17161/kjm.voll6.19669>

INTRODUCTION

Anthracyclines are effective and widely used chemotherapeutic agents, but their inherent properties confer cardiotoxic risk.¹ Echocardiographic changes in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) have served as primary surveillance for monitoring impaired cardiac function following anthracycline use.^{2,3} However, echocardiographic imaging is not always capable of elucidating the underlying mechanism of heart failure (HF) and may affect patient management and outcome in instances where multiple HF risk factors co-exist.

Atrial fibrillation (AF) is another well-known exacerbator of left ventricular (LV) dysfunction, primarily due to tachycardia-induced LV strain and perturbations in diastolic filling. However, the relationship between AF and HF is complex with each contributing to the pathophysiology of the other.⁴ As such, it can be easy to dismiss AF as a potential cause of HF in patients with more obvious explanations, particularly in patients with rate-controlled AF.

Cardiac magnetic resonance (CMR) imaging techniques such as T1 mapping and late gadolinium enhancement (LGE) have emerged as strategies for detecting substrate changes more specific to anthracycline therapy, including extracellular volume expansion and LV fibrosis.⁵ In patients with multiple possible causes of HF, CMR may play an essential role in elucidating the underlying mechanism and properly guiding HF management.

This case describes a patient with presumed anthracycline-induced cardiomyopathy with subsequent LVEF recovery following AF and atrial flutter (AFL) ablation and discusses the value of CMR in differentiating anthracycline-induced cardiomyopathy from other non-ischemic causes of HF.

CASE REPORT

A 77-year-old man with a past medical history of hypertension, coronary artery disease (CAD), and diffuse large B-cell lymphoma treated with six cycles of rituximab-cyclophosphamide-hydroxydaunorubicin-

oncovin-prednisone (R-CHOP) was referred to cardio-oncology for HF exacerbation, presumed to be secondary to anthracycline therapy. Depressed LVEF (45%) was first detected five months after completion of the R-CHOP regimen during an unrelated hospital stay; LVEF previously was normal at the start of chemotherapy (Figure 1). At the time of diagnosis, the patient was started on guideline-directed medical therapy (GDMT), including carvedilol, candesartan, spironolactone, and torsemide, and repeat coronary angiography revealed non-obstructive CAD. During his inpatient stay, he was diagnosed with new-onset AF and started on amiodarone to restore normal sinus rhythm (NSR).

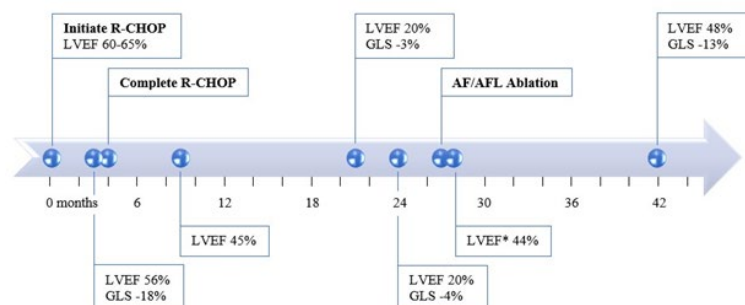


Figure 1. Timeline of key events and evolution of cardiac function, from initiation of R-CHOP therapy to 15 months post-ablation.

*LVEF was determined by CMR. All other LVEF values and GLS scores were obtained using transthoracic echocardiography. AF = atrial fibrillation. AFL = atrial flutter. CMR = cardiac magnetic resonance. GLS = global longitudinal strain. LVEF = left ventricular ejection fraction. R-CHOP = rituximab-cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone.

One year later, the patient presented to cardio-oncology with New York Heart Association (NYHA) Functional Class III symptoms and an LVEF of 20%. Electrocardiogram (ECG) performed at subsequent office visits demonstrated rate-controlled AF. Due to the severity of his symptoms and history of anthracycline therapy, the patient was referred for cardiac transplant evaluation, but was deemed a poor candidate due to advanced age and frailty.

He subsequently was referred to the electrophysiology clinic for consideration of an implantable cardioverter defibrillator (ICD) for primary prevention for persistent low LVEF despite maximally tolerated GDMT. Amiodarone was discontinued due to lack of rhythm control and the decision was made to pursue catheter ablation for AF/AFL. He underwent pulmonary vein isolation with additional posterior wall and cavotricuspid isthmus ablation. One-month post-ablation, the patient had significant LVEF recovery accompanied by an improvement in HF symptoms.

ECG-gated fast imaging employing steady-state acquisition (FIESTA) CMR was performed one-month post-ablation and revealed an LVEF of 44% and an absence of LV fibrosis by LGE, thereby excluding anthracycline-related cardiac damage (Figure 2). Fifteen months post-ablation, a transthoracic echocardiogram showed an LVEF of 48% with corresponding improvement in GLS to -13%, from a low of -3% prior to ablation. Indirect markers of cardiac function also showed improvement within one month of ablation. These markers included serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine, and diastolic pulmonary artery (PA) pressure as detected by an implantable CardioMEMs device (Figure 3B-D). ECGs performed at routine office visits following catheter ablation demonstrated normal sinus rhythm with an average heart rate between 60-65

bpm, approximately 30 points lower than pre-ablation ECGs (Figure 3A).

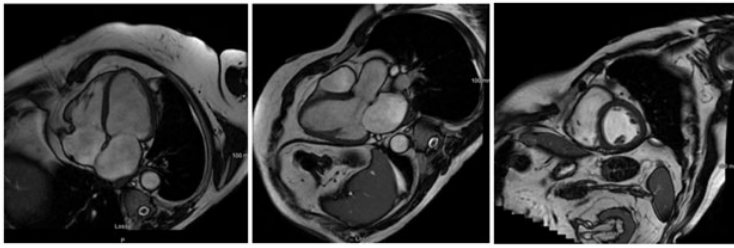


Figure 2. CMR images demonstrated an absence of LV fibrosis. CMR = cardiac magnetic resonance. LV = left ventricular.

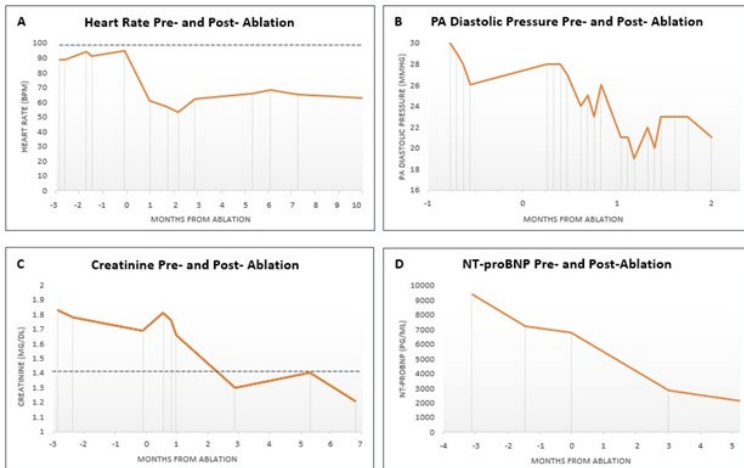


Figure 3. Changes in heart rate (A) and indirect markers of cardiac function (B-D) following catheter ablation for AF/AFL. (A) Pre-ablation ECGs demonstrated AF with controlled ventricular rates; post-ablation ECGs revealed NSR with an average heart rate of 61 bpm. (B) PA diastolic pressure was elevated prior to ablation and subsequently stabilized to an average of 21 mmHg one-month post-ablation. (C) Serum creatinine was elevated pre-ablation and subsequently decreased to normal range within two months of ablation. (D) NT-proBNP was elevated pre-ablation and subsequently decreased post-ablation.

AF = atrial fibrillation. AFL = atrial flutter. ECG = electrocardiogram. NSR = normal sinus rhythm. NT-proBNP = N-terminal pro-B-type natriuretic peptide. PA = pulmonary artery.

DISCUSSION

Heart failure following anthracycline-based chemotherapy is not uncommon, with incidence ranging from 3% to 26% depending on the cumulative dose and duration of follow-up.^{2,6} The risk of clinical HF is elevated in patients more than 65 years old with pre-existing cardiovascular conditions, and typically presents within one year of chemotherapy completion.

Advanced cardiac imaging, such as CMR, has emerged as a powerful tool capable of elucidating the underlying mechanism of anthracycline-induced cardiomyopathy (i.e., intra-cardiomyocyte edema and extracellular fibrosis).⁷ In patients with multiple risk factors for HF, CMR has the potential to differentiate anthracycline-induced cardiomyopathy from other non-ischemic causes of HF, such as AF, and may play an essential role in guiding HF management and improving patient outcomes.^{8,9}

Recent studies have explored the prognostic value of CMR in predicting LVEF improvement following AF ablation in patients with non-ischemic heart failure with reduced ejection fraction (HFrEF).^{5,10} The absence of LV fibrosis, as detected by LGE and T1 extracellular volume fraction mapping, has been shown to correlate with greater

improvement in LV systolic function following AF ablation. As such, CMR may play an additional role in predicting which patients are likely to have a favorable response to catheter ablation, thereby risk-stratifying patients based on the likelihood of clinical improvement and allowing for improved shared decision-making.

Pharmaceutical-based rhythm control has not been shown to improve clinical outcomes in patients with AF and HFrEF.¹¹ However, several recent studies have explored the superiority of ablation-based rhythm restoration. A meta-analysis comparing several randomized-controlled trials revealed significant improvements in LVEF, decreased number of hospitalizations, and reduced mortality in patients receiving catheter ablation for AF compared to those managed with medical therapy alone.¹² In patients with HFrEF and rate-controlled AF, an impaired systolic function may be more heavily dependent on diminished ventricular preload and irregular filling times; therefore, restoration of sinus rhythm may be even more critical to improvement in LV systolic function.

CONCLUSIONS

Rate-controlled atrial fibrillation is an important and easily overlooked cause of HFrEF in patients with a history of anthracycline use. Ablation-based rhythm restoration may be helpful in AF patients with controlled ventricular rates. Cardiac magnetic resonance imaging can be used to differentiate anthracycline-induced cardiomyopathy from other non-ischemic causes of HF and further can predict LVEF recovery in certain patient populations.

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Keywords: heart failure reduced ejection fraction, anthracyclines, left ventricular ejection fraction, atrial fibrillation, cardiac imaging techniques